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DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1956

ORIGINAL ARTICLES

TWO KINDS OF RENAL HYPERTENSION*

By Thomas Findley, M.D.
PROFESSOR OF MEDICINE (CARDIOVASCULAR RESEARCH)

(From the Department of Medicine and the Georgia Heart Association Laboratory for Cardiovascular Research, Medical College of Georgia, Augusta, Georgia)

Many remember the rosy glow that hovered over every sphygmomanometer following the publication in 1934 of Goldblatt's classic method for producing sustained diastolic hypertension in animals and the subsequent re-discovery of renin in Cleveland and Buenos Aires. The expected therapeutic triumph has not yet appeared, however, and it is fair to say that the patient with uncomplicated hypertensive vascular disease is probably no better off today than he was then.

It is not for want of effort, though, that the origin of this disorder seems as obscure as ever. Ingenious and even profitable attempts have been made to implicate the psyche, the hypothalamus, the autonomic nervous system and certain endocrine glands in its genesis, but somehow all roads return to the kidney. Oddly enough, there is still no agreement as to whether constriction of the renal artery, for example, results in hyper- or hypo-function of the kidney insofar as the ensuing hypertension is concerned. An explanation by analogy suggests itself, however. One is reminded of the fact that hyperglycemia of pancreatic origin may be due either to lack of insulin or to excess of glucagon, so even the pancreatectomy of von Mering and Minkowski was not the simple experiment it seemed to be when insulin first came to light. It begins to look as though high blood pressure may result from two kinds of renal dysfunction.

HYPER-RENAL HYPERTENSION. The idea that hypertension is due to an excess of circulating vasoconstrictor material emanating from the kidney is simple and attractive. This is so, chiefly because abrupt disturbances in renal blood flow produce such an excess and because nephrectomy occasionally reduces blood pressure. When one is faced with two alternatives, however, it is probably wise to choose not the one for which there is the greater number of arguments but that one against which there are the fewer objections. Certainly the case for *hyper-renalism* became less persuasive when several investigators independently produced hypertension by bilateral nephrectomy.

The complicated system of enzymes and substrates known here in the in-

*Read before the American Clinical and Climatological Association, Hot Springs, Va., November 2, 1955.

terest of simplicity as *renal pressor substance* (RPS) must have some function, however. The literature on the subject is enormous and controversial but from it one gets the impression that it is easier to find an excess of circulating RPS in shock, hemorrhage, heart failure and other conditions characterized by low blood pressure than it is in the hypertensive state. In addition to raising blood pressure, RPS increases the renal filtration fraction and maintains renal arteriovenous oxygen difference through a wide range of renal blood flow. Teleology is a dangerous word but the evidence justifies the conclusion that the renal tubule participates in a homeostatic response to circulatory failure by liberating a substance which bolsters arterial pressure, maintains glomerular filtration in the face of diminishing renal blood flow, and adjusts the appetite of the kidney for oxygen to the available supply.

The reason why a potentially useful reaction like this occasionally persists and becomes a menace in its own right is presumably related to extra-renal mechanisms, since removal of the offending kidney has such an unpredictable effect upon blood pressure. Improved diagnostic criteria, particularly the introduction of renal arteriography, have somewhat increased the percentage of good results from nephrectomy, and all of us feel indebted to Howard for his contributions to this field[5]. Even so, less than half of the hypertensive patients who had a kidney removed for unilateral disease at the Mayo Clinic[1] and the Ochsner Clinic[7] were helped manometrically, results quite in line with those reported two years ago by Schaffer[9]. The surgical statistics cannot, of course, deal with all the other individuals with hypertension and unilateral renal disease who are not operated upon for one reason or another, and if these are in turn diluted with all patients with bilateral renal disease and normal blood pressure, the frequency of hyper-renal hypertension becomes very small indeed. And yet I must admit that the only patients I have seen cured of malignant hypertension have been treated by nephrectomy.

HYPO-RENAL HYPERTENSION. It seems significant to me that, when clinical hypertension is associated with demonstrable renal disease at all, the kidneys are small and not large, a circumstance consistent with the appearance of hypertension in bilaterally nephrectomized animals kept alive by peritoneal dialysis[4] or parabiosis[6]. At present it is impossible to decide whether this comes about because normal kidneys excrete, destroy or inhibit the production of pressor substances from extra-renal sources or whether they secrete depressor material. All I intend to do is to describe a few nebulous clues which suggest that the renal tubule normally inhibits the anterior pituitary-adrenocortical machine.

An impressive piece of evidence has just been reported before the American Heart Association in New Orleans by Skelton[10] who found that malignant hypertension develops in young rats subjected to uni-nephrectomy, uni-adrenalectomy and radical enucleation of the other adrenal. So far as I know, this is the first time that steroid hypertension has been produced by intrinsic mechanisms only and is certainly a convincing demonstration that the adrenal cortex may be implicated in spontaneous disease. With Skelton we are examining adrenal vein blood from these animals to see whether the regenerating cortex secretes steroids in abnormal kind or quantity. The other part of this phenomenon which interests me particularly is the fact that uni-nephrectomy and a high sodium intake are absolutely necessary features. Once

again the protective influence of normal renal epithelium is demonstrated, and this leads to another clue which may or may not be meaningful.

Several years ago we reported that a number of procedures which disturbed the blood supply to the kidney also induced eosinophilia of the anterior pituitary[11]. Dogs rendered hypertensive by renal artery clamps showed an increase in eosinophils from a normal value of 40% to a level of about 70%, and similar increases followed complete occlusion of both the renal artery and vein for short periods of time. At first we were inclined to attribute this to the stimulating effect of RPS, but the pituitaries of bilaterally nephrectomized hypertensive dogs kindly sent to us by Grollman showed the same changes. We inferred, therefore, that renal tubules normally inhibit the acidophilic elements of the anterior pituitary. I am sorry that we have no biologic evidence to show that these cells are secreting increased amounts of renotrophin but endocrinologists seem to accept the "feed-back" principle when applied, for example, to the increased output of trophic pituitary hormones induced by castration or by thyroidectomy. When one kidney is badly damaged or entirely removed its mate enlarges and this "compensatory" hyperplasia is probably due to growth hormone or to something not yet separated from it. Essential hypertension could be caused by an enzymatic defect in the renal tubule which renders it insensitive to these trophic influences. The whole process might represent a homeostatic response designed to repair a threatened kidney; the reaction persists simply because the kidney cannot respond. Ultimately vascular lesions of hormonal origin appear and the organism destroys itself. Once more the hope of substitution therapy appears.

Finally, there is evidence of altered sodium metabolism in the common idiopathic variety of hypertenisve vascular disease. In Cushing's syndrome the renal tubules reject a surprisingly large fraction of the salt offered to them in glomerular filtrate. Birchall *et al.*[2] found that this phenomenon occurred in essential hypertension also, but to a lesser extent, and that normotensive subjects behaved this way after small doses of cortisone. Furthermore, in hypertension the kidney responds abnormally to the Hickey-Hare test, a procedure which measures the ability of hypertonic saline infusions to inhibit water diuresis. In Cushing's syndrome the diuresis proceeds undisturbed much as it does in diabetes inspidus, and in essential hypertension the antidiuretic effect is only moderate. Thus, the capacity of the renal tubule of the hypertensive subject, with or without Cushing's syndrome, to resorb normal amounts of salt and water is limited and resembles that of a normal subject receiving cortisone in doses too small to produce hypertension or edema. Farnsworth[3] had previously reported that the tubular resorption of chloride is impaired in hypertension. All of this seems paradoxical and obscure, especially in the light of the demonstration by Perera and Blood that hypertensive patients tolerate salt restriction better than normals do[5]. There is some evidence that the hypertensive individual is abnormally sensitive to parenteral DOCA and it is well-known of course that this substance produces sodium diuresis in Cushing's syndrome.

Summary. Hypertension due to excessive secretion of a renal pressor substance probably exists but must be rare.

Hypo-renalism is a more satisfactory explanation for human and experimental forms of hypertensive vascular disease. A deficit of renal tubular mass or function probably elicits a response

from the anterior pituitary-adrenocortical axis because a) bilateral nephrectomy induces eosinophilia of the anteprior pituitary, b) enucleation of the adrenals produces hypertension only in a uninephrectomized animal and c) the kidney in human hypertension handles salt and water loads in the same manner as in Cushing's syndrome.

Human hypertension could be due to a metabolic defect in renal tubular epithelium which renders it insensitive to trophic influences of anterior pituitary or adrenocortical origin.

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SUMMARIO IN INTERLINGUA

Duo Species de Hypertension Renal

Hypertension causate per excessive secretion de un renal substantia pressoral existe probabilemente sed debe esser rar.

Hypo-renalismo es un plus satisfacente explication de formas human e experimental de hypertensive morbo vascular. Un deficit de massa o de functionamento reno-tubular evoca probabilemente un responsa ab le axe anteropituitari-adrenocortical proque (a) nephrectomia bilatere induce eosinophilia del glandula pituitari anterior, (b) enucleation del adrenales produce hypertension solmente in animales uninephrectomisate, e (c) le renes in hypertension human tracta cargas de sal e aqua in le mesme maniera que in syndrome de Cushing.

Hypertension human es possibilemente le resultato de un defecto metabolic in le epithelio tubular renal que rende lo insensibile a influentias trophic de origine anteropituitari o adrenocortical.

CLINICAL VALUE AND SIGNIFICANCE OF UNIPOLAR RIGHT ARM LEAD IN HYPERTENSION

By Desiderio Gross, M.D.
SANTIAGO, CHILE

It has long been known that arterial hypertension is reflected in the electrocardiogram. The respective changes were first described in standard leads and later in thoracic ones. On the contrary, the corresponding alterations in unipolar extremity leads have been investigated only quite recently. It has been established that all changes which occur in the electrogram are caused essentially by left ventricular hypertrophy and strain. Increase in voltage of the R wave, flattening or inversion, or both, of T wave combined with a depressed S–T segment, widening of the QRS interval in lead I accompanied by similar but oppositely directed changes in lead III are the common features of this frequently observed pattern. Evans, Mathews and White[4] have made a detailed study of the most important changes occurring in arterial hypertension both in standard and thoracic leads; they have found significant correlations between the electrocardiographic alterations and both clinical and laboratory aspects (eyeground, Roentgen-ray, renal biopsy). However, their studies did not comprise unipolar limb leads. Changes in hypertension have indeed often been found in unipolar limb leads; but this aspect has not yet been systematically investigated. Goldberger[7], in the 3rd edition of his classical textbook on unipolar lead electrocardiography, refers only incidentally to this point.

Because of the frequently observed alterations in the unipolar right arm lead in cases of hypertension, I have undertaken a systematic search for correlations between clinical conditions and the electrocardiographic aspects. As a result, definite correlations were found between clinical conditions and right arm lead, and also RV lead and thoracic leads V_4 and V_6.

The unipolar right arm lead presents some peculiarities and differs from other unipolar limb leads. Whereas the left arm and left leg leads face the epicardial surface of the heart, the right arm lead faces the heart cavities. It thus registers chiefly changes in the electrical potential of the endocardial surface. Thanks to this circumstance the right arm lead can furnish valuable information concerning electrical events that occur within the heart; with some exaggeration the unipolar right arm lead can be considered as a sort of intracardiac electrocardiographic catheterization.

The right arm lead resembles the direct intracavitary lead registered at high auricular level (Hecht[9], Battro and Bidoggia[1], Sodi-Pallares, Vizcaino, Soberon and Cabrera[12], Gilbert-Queralto, Torner-Soler, Paravasini and Morato-Portell[6].) The right shoulder is, according to its spatial orientation, a fixed electrode facing the internal surface of the anterolateral cardiac wall of the left ventricle. However, it registers also all electrical events in intercepted structures such as the right ventricle and the interventricular septum. Consequently, the VR lead explores an extensive zone of the endocardial surface of different parts of the heart which influence in a different

manner the electrocardiographic aspect with this lead.

Our experiments suggested that information from a unipolar right arm lead can be much increased when the outer surface of the corresponding zone of the cardiac wall is also explored by unipolar thoracic leads opposite to the right arm lead. In effect, the combined examination of VR and V_6 has furnished many useful data concerning the functional condition of the myocardial zone between the two exploring electrodes. However, the unipolar right arm lead registers an extensive zone and is, therefore, less definitive; the thoracic lead explores a smaller area and thus gives a more concise information. By using both these electrocardiographic leads we obtain more precise data regarding the functional condition of the myocardium beneath the epicardial surface. Data concerning the endocardial surface obtained by means of lead VR are less precise. As will be demonstrated, both leads are interrelated; but they are of greater value when used together.

The present paper describes the results obtained with the systematic use of VR and V_6 leads in healthy subjects, and in patients with hypertension or with bundle branch block.

Materials and Method. The tracings were registered with a Sanborn *instomatic* electrocardiograph with the patient in recumbent position. The standard, three unipolar extremity (Goldberger) and three unipolar thoracic leads were inscribed in positions C_2, C_4 and C_6. In the group of patients with hypertension the position of the electrical axis, angle alpha, was determined by means of the chart devised by Carter and associates[2] and by the formula of White and Bock[14]. The author's strain index[8] was calculated also in every case. The heart size was estimated fluoroscopically by a rather rough practical procedure; it was classified as normal, or slightly (+), moderately (++) or considerably (+++) enlarged.

The ventricular complexes in VR lead were classified in 5 groups as follows (Fig. 1):

Pattern No. 1 T negative, ST isoelectric
" No. 2 T negative, ST elevated.
" No. 3 T isoelectric, ST isoelectric
" No. 4 T positive, ST isoelectric.
" No. 5 T positive, ST elevated.

Separate groups of healthy subjects, cardiac patients with hypertension divided into 5 groups according to the 5 VR patterns observed, and cardiac patients with left and right bundle branch block were studied. Each group contains 30 observations. A comparison was made between the calculated averages of the 5 groups.

Results. HEALTHY INDIVIDUALS (Table 1). The average age was 43.2 years, with a range from 13 to 71 years. The average blood pressure was 118/77 mm. Hg, and the heart size was normal in every case. The VR lead always showed a negative T wave and an isoelectric ST segment. The ventricular complex presented a QS pattern in 21 cases (70%), a QR pattern in 5 cases (17%) and an RS pattern in 4 cases (13%). It was not possible to obtain a definite correlation between the ventricular pattern in the VR lead and the electrocardiographic position because the same pattern was present with equal frequency in opposite electrocardiographic positions. Thus, the QS pattern was present in 7 cases in vertical position but also in 7 instances in cases of horizontal position. T_6 and T_4 were positive in 100% of the observations.

CARDIAC PATIENTS WITH HYPERTENSION. *Pattern No. 1* (Table 2). The average age was 51.3 years, ranging from 37 to 67 years. Average blood pressure was 173/102 mm. Hg. The position of the electrical axis expressed in angular degrees averaged +5.66°, ranging from +75° to −66°. The formula of White and Bock gave an average of +11.25, with a range from −5.5 to +26.0. The strain index measured +9.4, with a range from −6.0 to

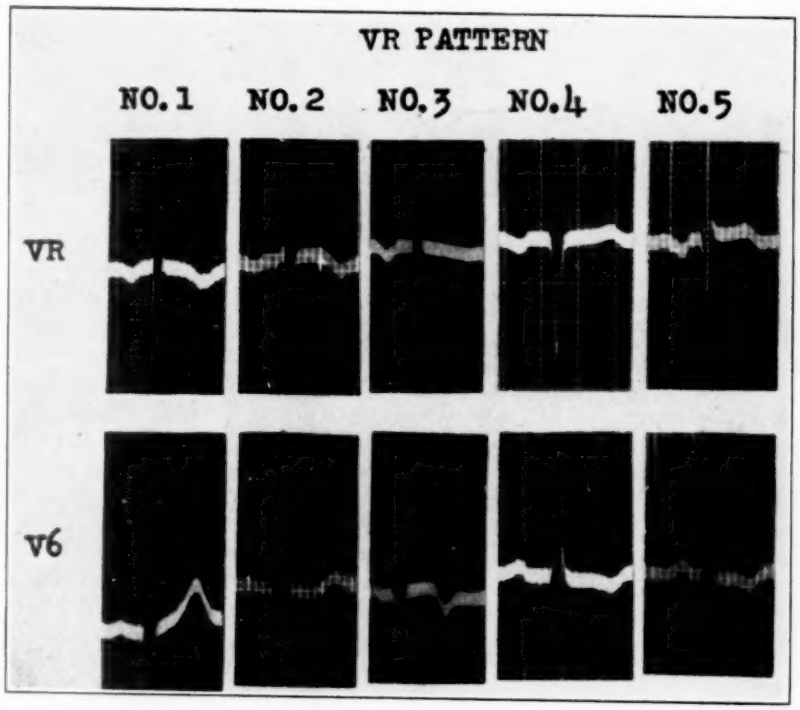

Fig. 1.—The five VR patterns and the corresponding V_6 leads in cases of hypertension.

TABLE 1.—HEALTHY SUBJECTS

Age (Yr.)	*Blood Pressure mm.Hg*	*Heart Size (+)*	*VR Pattern*	T_1	T_6
43.2	118/77	0	No. 1 (100°/°)	+(100°/°)	+(100°/°)

TABLE 2.—HYPERTENSIVE CARDIAC PATIENTS

VR Pattern	*Age (Yr.)*	*Blood Pressure mm.Hg*	*Angle (°)*	*White and Bock Formula*	*Strain Index*	*Heart Size (+)*	T_1	T_6
No. 1	51.3	173/102	+ 5.66	+11.25	+ 9.4	0.27	+100°/°	+100°/°
No. 2	61.0	172/96	+10.0	+16.6	+18.6	0.75	96.7°/° iso. 3.3°/°	+100°/°
No. 3	58.0	176/115	−10.8	+20.17	+23.9	0.87	+100°/°	−80°/° iso. 20°/°
No. 4	54.9	180/108	− 1.35	+20.27	+30.8	1.15	+85°/° −15°/°	−90°/° +10°/°
No. 5	54.0	190/116	− 2.4	+21.83	+32.2	1.60	+80°/° −20°/°	−90°/° iso. 7°/° + 3°/°

+27.0. T_6 and T_4 were positive in all cases. The average heart size was 0.27+.

Pattern No. 2. The average age was 61.0 years, with a range from 38 to 77 years. The blood pressure averaged 172/96 mm. Hg. Angle alpha presented an average of +10.0°, with a range from +56° to −37°. The formula of White and Bock gave an average of +16.6, with a range from +2.0 to +32.0. The strain index measured +18.6, with a range from +1.0 to +48.0. The T wave in lead V_6 was positive in 100% of the cases; T_4 was positive in 29 cases (96.7%) and isoelectric in one case (3.3%). The average heart size was 0.75+.

Pattern No. 3. The average age was 58.0 years, ranging from 47 to 68 years. Average blood pressure measured 176/115 mm. Hg. Angle alpha presented an average of −10.8°, with a range from +30° to −40°. The White and Bock formula gave an average of +20.17, with a range from +6.5 to +30.0. The strain index averaged +23.9, with a range from +6.0 to +40.0. T_6 was negative in 24 cases (80%) and isoelectric in 6 cases (20%). T_4 was positive in all cases. The average heart size was 0.87+.

Pattern No. 4. The average age was 54.9 years, ranging from 48 to 61 years. Blood pressure was 180/108 mm. Hg. Angle alpha presented an average of −1.35°, with a range from +35° to −38°. The White and Bock formula gave an average of +20.27, with a range from −4.5 to +38.0. The strain index was +30.8, with a range from +7.5 to +52.0. T_6 was negative in 27 cases (90%) and positive in 3 cases (10%). T_4 was positive in 25 cases (85%) and negative in 5 cases (15%). The average heart size was 1.15+.

Pattern No. 5. The average age was 54.0 years, ranging from 40 to 68 years. Average blood pressure was 190/116 mm. Hg. Angle alpha showed an average of −2.4°, with a range from +57.0° to −35.0°. The White and Bock formula gave an average of +21.83, with a range from −1.0 to +37.5. The strain index was +32.21, with a range from +5.0 to +68.5. T_6 was negative in 27 cases (90%), isoelectric in 2 cases (6.7%) and positive in one case (3.3%). T_4 was positive in 24 cases (80%) and negative in 6 cases (20%). The fluoroscopic heart size averaged 1.6+.

BUNDLE BRANCH BLOCK (Table 3). *Left.* The average age was 65.2 years, ranging from 40 to 76 years. Blood pressure averaged 138/82 mm. Hg. VR lead presented in all cases pattern No. 5. This uniform VR pattern was combined also with a unique form of V_6 pattern: T_6 was negative in 100% of the cases. V_4 presented a different behavior: it was negative only in 6 cases (20%) and positive in 24 cases (80%). The average heart size was 0.73+.

Right. The average age was 63.8 years, ranging from 36 to 82 years. The VR lead presented pattern No. 1 in 24 cases (80%), pattern No. 2 in 4 cases (13.3%) and pattern No. 5 in 2 cases (6.7%). With pattern No. 1, T_6 was positive in 100%, whereas T_4 was positive in 22 out of 24 cases (91.6%) and negative in 2 cases (8.4%). With pattern No. 2, T_6 was isoelectric and positive in an equal proportion, there being 2 cases in each group. With pattern No. 5, both T_6 and T_4 were negative in every instance (100%). The fluoroscopic heart size averaged 0.66+.

Discussion. The unipolar right arm lead registers the cavity potential of the heart which is always negative in cases of normal activation. This experimentally observed fact is unquestioned. There is no place here for suggestions, as made recently by various authors, for example, Fumagalli[5], who proposed replacing the VR lead in clinical prac-

tice by an inverted VR, for a more rational arrangement of electrodes representing the frontal plane. Direct observations have shown that during the inscription of QRS a negative cavity potential arises, due to the spread of excitation toward the epicardial surface of the ventricular wall. As a result, the normal VR lead presents a ventricular complex with its main deflection directed downward and a negative T wave.

It is evident that the configuration of the VR lead is mainly determined by the functional state of the opposite myocardial wall, that is, the antero-endocardial surface. In pattern No. 3 the epicardial surface already shows changes revealed by leads V_6 and V_4. Lead V_6, because of its anatomical position, and because it represents principally the apical region of the left ventricle, is evidently a more sensitive index of the functional state of the myocardium subjacent to the epicardial surface and is more closely related to VR than to V_4. Despite definitively pathological complexes, T_4 remained normal, that is, positive, in 100% of the cases, whereas T_6 was negative in 80% and positive in 20% only. A similar situation was observed in the group

TABLE 3.—CARDIAC PATIENTS WITH BUNDLE BRANCH BLOCK

	VR Pattern	*Age (Yr.)*	*Blood Pressure (mm.Hg)*	*Heart Size (+)*	T_4	T_6
Left	No. 5 (100%)	65·2	138/82	0·73	−20% +80%	−100%
Right	No. 1 (80%)	63·8	140/88	0·66	+91·6% −8·4%	+100%
Right	No. 2 (13·3%)				iso. 50% −50%	iso. 50% +50%
Right	No. 5 (6·7%)				−100%	−100%

lateral region of the left ventricle. As the VR lead is an essentially indirect, intracavital lead, it faces the endocardial surface of the heart, but the epicardial surface of the same area also exerts its modifying influence. This can be clearly demonstrated by observations made in our patients with hypertension. Thus, in cases of VR pattern No. 1, both cardiac surfaces were normal, with T_6 and T_4 positive in every case. In the presence of pattern No. 2, the VR lead presented an elevated ST segment, but the epicardial leads V_6 and V_4 remained quite normal with the T wave positive in both positions. This pattern apparently represents an initial stage of change confined to the with pattern No. 4 wherein the less sensitive V_4 lead presented a positive T wave in 85%, in contrast to lead V_6 wherein T_6 was negative in 90% of the cases. Finally, in the group with pattern No. 5, V_4 remained normal in 80% of the cases, in contrast to V_6 which presented abnormal features in 97%, the wave being negative in 90% and isoelectric in 7%.

From observations made in the group of patients with hypertension it can be concluded that between VR and V_6 leads, that is, between the leads representing endocardial and epicardial potentials respectively of corresponding areas of the cardiac wall, the following correlation holds: in cases having

a negative T wave, with or without an elevated ST segment, in the VR lead, V_6 presents a positive T wave. In cases with an isoelectric T wave in lead VR, T_6 is overwhelmingly (80%) negative. Finally, when the T wave in VR is positive, with or without an elevated ST segment, T_6 is practically always negative (90%) though it may be isoelectric (7%).

It appears evident from these studies that, in hypertensive conditions, the first changes develop in lead VR, and consist in an elevation of the ST segment without simultaneous modifications in the thoracic leads. This finding would suggest that hypertension first causes changes in the subendocardial and only later in the subepicardial region of the ventricular myocardium. Such an opinion is in accordance with experimental facts registered by Johnson and DiPalma[10] who found that during systole, the intramyocardial pressure rises much more in the deeper layers of the myocardium of the left ventricle than in the superficial zone. Increased intramyocardial pressure may impair the blood supply of the subendocardial myocardium and thereby account for the observed electrocardiographic changes.

A comparison between leads V_4 and V_6 reveals that alterations due to hypertension appear earlier, more often and more intensely in lead V_6 than in lead V_4. This fact may be explained by the more pronounced hypertrophy and strain in the part of the left ventricle having the thickest wall, that is, the apical region. Both in normal cases and in the initial stages of hypertension, there is no difference in the electrical behavior of the myocardium of the cardiac apex and that of the neighboring region. The cardiac apex is located normally in thoracic position C4; in fact, in both conditions the T wave is as positive in lead V_4 as in V_6. In cases of advanced hypertension with consequent hypertrophy and dilatation, in addition to positional changes, the cardiac apex is usually displaced to the left, and, thus, the electrical events occurring in the apical region can be recorded better in position C6 than in C4.

Correlations between the five VR patterns previously described and other electrocardiographic and clinical data have been carefully examined. The following conclusions emerge:

AGE. No correlations between average age and the VR pattern could be established.

BLOOD PRESSURE. The average systolic blood pressure showed a slight tendency toward correlation with the magnitude of alterations in the VR lead. The average systolic blood pressure was practically identical in the groups with pattern Nos. 1, 2 and 3, being 173, 172 and 178 mm. Hg respectively. In the group with VR pattern No. 4 it was 180 mm. Hg. The highest average systolic blood pressure of 190 mm. Hg, was found in the group with pattern No. 5. The behavior of the average diastolic blood pressure was irregular and no conclusions could be drawn.

POSITION OF THE ELECTRICAL AXIS. ANGLE ALPHA. No strict correlation could be established between the VR pattern and the position of the QRS electrical axis. In cases of pattern Nos. 1 and 2 this angle presented values of $+5.66°$ and $+10.0°$ respectively. With a progressive involvement of the myocardium, as expressed by patterns Nos. 3, 4 and 5, the direction of the average angle alpha deviated to the left but not in a quantitative order. Thus, the direction of the average angle alpha in the group with pattern No. 3 exhibited the most pronounced shift to the left, namely, $-10.8°$. In the groups with pattern Nos. 4 and 5 the angle alpha showed a lesser deviation to the left,

its corresponding average position being $-1.35°$ and $-2.4°$ respectively. This lack of strict correlation between the electrocardiographic pattern and the position of the electrical axis indicates that the condition of the myocardium, as expressed by the VR pattern, is only one of the many factors determining the position of the electrical axis.

FORMULA OF WHITE AND BOCK. According to White and Bock, an abnormal degree of left axis deviation is present when their formula (R1 + S3) − (R3 + S1) is greater than +30.0. In the present study the numerical requirements of an abnormal left axis deviation were not fulfilled as far as *average* values were concerned. On the other hand, a clear-cut numerical parallelism could be established between the White and Bock formula and the VR pattern. In the group of patients with pattern No. 1, the White and Bock formula averaged +9.4 with a maximum of +27.0. In the successive groups of pattern Nos. 2, 3, 4 and 5 the average index increased to +16.0, +20.17, +20.27 and +21.83 respectively with a maximum range in each group greater than +30.0.

THE AUTHOR'S STRAIN INDEX. In a recent paper the author introduced a formula ([R1 − S1] − 2T1) + ([S3 −R3] + 2T3) that expresses quantitatively the degree of ventricular myocardial involvement associated with strain. This formula combines alterations of the QRS complex and of the T wave in leads I and III in a single expression: "the strain index." In normal cases it amounts ±12.5; in cases of left ventricular strain it is always positive with a mean value of +47.2 and a range of +32.5 to +79.5. In cases of right ventricular strain it is negative with a mean value of −27.6 and with a range of −20.0 to −40.0. As seen in Table 2, the strain index offers a remarkable parallelism with the condition of the left ventricular myocardium as expressed by the unipolar right arm lead pattern and the fluoroscopic heart size. In effect, the strain index in the group with VR pattern No. 1 was +9.4; in the group with pattern No. 2 it was +18.6, and in the successive groups of patterns, Nos. 3, 4 and 5 respectively it amounted to +23.9, +30.8, and +32.2. It follows that in hypertension the severity of myocardial damage arising from this condition can be recognized and estimated as much by the VR pattern as by the author's strain index. Both criteria present an adequate parallelism with clinical data and with each other.

HEART SIZE. The results of roentgenological measurements of the heart size, even when standard values are used for comparison, are not mathematically accurate. White[13] states that, "measurements of the heart should be interpreted very freely; they are probably better than no measurements at all, when they are so interpreted. But when an attempt is made to fit each case within narrow so-called standard limits, it is better to discard all measurements and to rely simply on general impressions and experience." The approximate estimation here employed satisfied the needs of the present investigation. The size as estimated by fluoroscopy was found to be proportional both to the VR patterns and to the corresponding strain index. The latter presented its smallest value in cases of normal or slightly enlarged hearts, and its highest value in cases where the heart shadow was maximally enlarged (+++). One may conclude that in cases of hypertension the unipolar right arm lead pattern, strain index and roentgenologic heart size are equivalent expressions of myocardial damage.

Comparison of the values of VR and

V_6 leads in cases of bundle branch block revealed interesting facts. In cases of left bundle branch block the VR lead showed, without any exception, pattern No. 5, and lead V_6 a negative T wave in 100%. In agreement with observations with V_4 lead in cases of hypertension, T_4 was negative in only 20% and positive in 80%, indicating that the V_6 lead is superior to V_4. Pattern No. 5 in the VR lead and a positive T_6, always present in cases of left bundle branch block, reveal that the determining factor of the electrocardiographic pattern in both leads is the *functional* condition of the myocardium and not necessarily its *anatomical* condition. In cases of left bundle branch block, the cavity potential of the left ventricle was found to be positive by all investigators, a situation opposite to the normal. The abnormal spread of excitation due to the interruption of the conduction in the left branch of the bundle of His provokes an inverted activation of the myocardium of the left ventricle. Electrocardiographic consequences of this abnormal state of activation in leads VR and V_6 are identical to those found in hypertension in the group with pattern No. 5. This identity suggests the possibility that, in advanced stages of hypertension, the electrocardiographic changes observed are due to initial degrees of left bundle branch block. This interpretation is supported by the explanation given by Coelho *et al.*[3] who investigated the left ventricular cavity potential in cases of left bundle branch block by means of retrograde catheterization; they found it to be positive, and associated with a positive T wave. The authors conclude that the presence of an incomplete left bundle branch block is responsible for the abnormal state of activation.

In cases of right bundle branch block, as would be expected, the situation was reversed. In 24 cases (80%) pattern No. 1 was encountered, and in 4 cases (13.3%) pattern No. 2 in the right arm lead. T was positive in 100% with VR pattern No. 1; with VR pattern No. 2, 50% were positive and 50% isoelectric. In 2 cases (6.7%) an unusual situation was observed, namely, the association of a negative T_6 with VR pattern No. 5. Consequently, it can be stated that activation of the left ventricular wall in cases of right bundle branch block occurs in the same manner as in normal cases with normal VR pattern No. 1 and positive T_6. Exceptions to the rule in these and other cases can be explained by simultaneously existing alteration of the neighboring structures which influence the general pattern. Pruitt, Burchell and Essex[11] have observed that the electrocardiographic consequences of subendocardial injuries depend upon the spatial orientation of the traumatized tissue with respect to the exploring electrode. In an epicardial lead the depression of the ST segment produced by a subendocardial injury of the free wall of the left ventricle disappeared almost completely when the same type of injury extended into the septum.

Summary. 1. The unipolar right arm lead and thoracic lead V_6 were systematically used to study the endocardial and epicardial surface potentials of the anterolateral wall of the left ventricle in normal cases, in hypertensive cases and in cases of bundle branch block. 2. Definite correlations could be established between the electrocardiographic aspects of VR and V_6 leads. The direction of the T wave in these leads is opposite. In cases of normal activation of the left ventricular wall, in the initial stages of hypertension, and in cases of right bundle branch block T_{VR} is negative and T_6 is positive;

whereas in advanced stages of hypertension and in cases of left bundle branch block T_{VR} is positive and T_6 is negative. 3. In cases of hypertension 5 different patterns were established according to the appearance of lead VR. Each pattern was correlated with the pertinent clinical data, roentgenologic heart size, position of the electrical axis and with the corresponding strain index. The VR pattern presented a direct correlation with the severity of myocardial damage caused by hypertension. Patterns Nos. 1 and 2 indicated initial, and patterns Nos. 4 and 5 advanced stages of myocardial involvement. 4. The unipolar right arm lead alone, and especially in combination with thoracic lead V_6, provides useful information regarding the condition of the left ventricular myocardium in cases of hypertension.

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(Interlingua on page 139)

RENAL RESPONSE TO PENTOLINIUM: LABORATORY OBSERVATIONS*

By John H. Moyer, M.D.
ASSOCIATE PROFESSOR OF PHARMACOLOGY AND MEDICINE

AND

Carroll A. Handley, Ph.D.
PROFESSOR OF PHARMACOLOGY

WITH THE TECHNICAL ASSISTANCE OF

Ann Hall

AND

Margaret Mazeika

(From the Department of Pharmacology, Baylor University College of Medicine, Houston, Texas)

The development of drugs which block the transmission of impulses over the autonomic nervous system has led to effective measures for reducing the blood pressure in patients with severe hypertension. In the development of these drugs, it is necessary to evaluate the effect on such vital vascular beds as the brain, the heart, and the kidneys. The latter is particularly important when studying drugs which are to be used for the treatment of hypertension. Prior to the clinical evaluation of these agents, it is advisable to study the responses to these drugs in laboratory animals. The following report is a laboratory study of the renal effect of pentolinium. In addition to the effects on blood pressure and renal hemodynamics, observations were also made on water and electrolyte excretion.

Methods. Eighteen female dogs ranging in weight from 11 to 21 kg. were used. These animals were anesthetized with pentobarbital, using 30 mg. per kg. body weight. Creatinine was used to measure glomerular filtration rate, para-aminohippurate was used to estimate renal plasma flow. Maximum tubular function was measured in 8 dogs by determining the maximum reabsorptive capacity for glucose (TmG). Sodium and potassium concentrations in the plasma and the excretion rates of these electrolytes were measured using a Beckman flame photometer for analysis. Except for minor modifications, the analytical methods have been described previously[1]. Mean blood pressure was determined by intra-arterial manometry. After three successive 10-minute control periods, 2 mg. per kg. of body weight of pentolinium were administered intravenously. Successive 10-minute periods were collected for 2 hours after administration of the drug. Intermittent observations on renal hemodynamics and water and electrolyte excretion are recorded in Tables 1 and 2. Three days after the initial observations on renal function in 10 dogs in which TmG was not determined, observations on glomerular filtration rate, renal blood flow and water and electrolyte excretion were again made. During the latter observations, the dogs were anesthetized similar to the methods employed during the initial observations. Three successive 10-minute periods were collected for the follow-up study. These observations served to rule out residual renal effects due to pentolinium.

Results. The renal hemodynamic effects of blood pressure reduction with pentolinium in 10 dogs on which maximum tubular function was not determined (Group 1) are recorded in Table 1A. There was a significant reduction

TABLE 1A—RENAL HEMODYNAMIC RESPONSE TO PENTOLINIUM IN DOGS

Mean Blood Pressure mm./Hg	Renal Blood Flow† ml./minute	Renal Vascular Resistance††	Hematocrit

*Supported in part by a grant from the Houston Heart Association.

TABLE 1A—RENAL HEMODYNAMIC RESPONSE TO PENTOLINIUM IN DOGS

	Mean Blood Pressure mm./Hg					*Renal Blood Flow† ml./minute*					*Renal Vascular Resistance††					*Hematocrit*				
Dog No.	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4
1	137	99	84	112	125	273	297	208	146	322	.50	.33	.40	.77	.39	33	30	25	28	40
2	132	78	104	156	162	376	411	278	246	476	.35	.19	.37	.63	.34	45	46	45	44	46
3	126	119	120	139	127	340	330	314	289	218	.37	.36	.38	.48	.58	50	47	44	44	40
4	126	92	87	76	101	178	140	120	85	207	.71	.66	.73	.89	.49	42	42	40	35	33
5	146	110	111	118	132	223	247	230	160	282	.65	.45	.48	.74	.47	40	43	43	43	35
6	120	88	71	121	140	224	258	213	123	192	.54	.34	.33	.98	.73	38	41	38	34	35
7	142	129	118	124	126	240	240	209	163	222	.59	.54	.56	.76	.57	50	48	45	38	37
8	117	72	64	77	146	375	325	345	173	400	.31	.22	.19	.45	.37	44	44	42	40	35
9	114	80	78	88	99	443	346	203	147	451	.26	.23	.38	.60	.22	35	32	27	27	26
10	144	110	107	117	...	268	248	222	186	...	.54	.44	.48	.63	...	35	35	33	35	...
Mean	130	98	94	113	129	294	284	234	172	308	.48	.38	.43	.69	.46	41	41	38	37	36
Per cent of Control		75	72	87	99		97	80	59	105		79	90	144	96		100	93	90	88
P Value <‡		001	001	.05	NS		NS	05	001	NS		001	20	001	NS		NS	05	05	NS

	Glomerular Filtration Rate ml./minute					*Renal Plasma Flow ml./minute*					*Filtration Fraction**				
Dog No.															
1	50	42	35	35	54	183	208	156	105	193	.27	.20	.22	.33	.28
2	62	60	63	63	68	207	222	153	138	257	.30	.27	.41	.46	.26
3	68	61	57	59	51	170	175	176	162	131	.40	.35	.32	.36	.39
4	42	32	27	27	52	103	81	72	55	139	.41	.40	.38	.49	.37
5	47	45	46	38	61	134	141	131	91	183	.35	.32	.35	.42	.33
6	50	45	40	34	52	139	152	132	81	125	.36	.30	.30	.42	.42
7	47	43	38	38	46	120	125	115	101	140	.39	.34	.33	.38	.33
8	48	38	35	25	59	210	182	200	104	260	.23	.21	.18	.24	.23
9	73	57	43	38	84	288	235	148	107	334	.25	.24	.29	.36	.25
10	28	25	25	24	...	174	161	149	121	...	.16	.16	.17	.20	...
Mean	52	45	41	38	59	173	168	143	107	196	.31	.28	.30	.37	.32
Per cent of control		87	79	73	113		97	83	62	113		90	97	119	103
P Value <‡		.001	.01	.01	.30		NS	.10	.01	.10		.01	.30	.10	NS

C = Control
D_1 = Immediately after drug was given (average of two 10-minute periods)
D_2 = One hour after drug was given (average of two 10-minute periods)
D_3 = Two hours after drug was given (average of two 10-minute periods)
D_4 = Follow-up 3 days after drug was given

† Renal Blood Flow = $\frac{\text{Renal Plasma Flow}}{1-\text{Hematocrit}}$

†† Renal Vascular Resistance = $\frac{\text{Mean Blood Pressure}}{\text{Renal Blood Flow}}$

* Filtration Fraction = $\frac{\text{Glomerular Filtration Rate}}{\text{Renal Plasma Flow}}$

‡ $t = \bar{x}\sqrt{\frac{n(n-1)}{S\bar{x}^2}}$

NS = $p > 0.30$

TABLE 1B—EFFECT OF PENTOLINIUM ON WATER AND ELECTROLYTE EXCRETION IN DOGS

	Urine Volume ml./min.					*Urine Sodium μEq./min.*					*Urine Potassium μEq./min.*					*Plasma Potassium mEq./L.*					*Plasma Sodium mEq./L.*				
Dog No.	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4	*C*	D_1	D_2	D_3	D_4
1.	1.0	1.1	0.9	0.9	1.1	13	12	7	9	45	61	46	28	19	45	3.8	3.6	3.6	3.5	2.6	135	137	137	138	145
2.	1.9	1.4	2.0	6.5	1.2	142	116	88	385	77	38	39	50	186	30	3.1	3.6	3.6	4.3	3.1	139	141	141	141	143
3.	0.6	2.6	2.3	3.8	0.4	123	222	169	309	40	28	29	24	90	13	3.4	3.4	3.3	3.5	3.4	130	130	134	136	151
4.	2.1	1.6	0.9	1.0	1.1	241	216	74	90	230	37	34	31	28	40	2.9	3.3	3.0	2.5	2.8	141	140	140	140	140
5.	0.6	1.0	1.5	1.2	1.6	33	84	41	24	36	22	32	32	22	45	3.3	2.9	2.7	2.7	2.7	136	135	143	143	141
6.	2.6	1.9	1.4	2.1	1.5	246	244	126	91	104	65	45	37	37	65	3.1	2.8	3.5	4.1	3.5	152	153	148	148	151
7.	1.7	2.4	1.2	2.7	3.0	155	253	116	114	220	24	32	25	54	37	3.1	3.0	3.6	3.5	3.0	141	139	141	141	150
8.	1.1	0.8	0.6	0.5	2.2	49	30	10	13	23	27	17	12	15	72	2.6	2.5	3.1	3.5	3.8	149	151	147	147	141
9.	3.6	2.4	1.0	0.8	1.9	422	223	40	28	144	51	45	23	21	44	2.7	2.6	2.8	2.6	2.9	145	148	148	148	146
10.	1.7	2.4	3.1	5.8	...	102	213	271	326	...	30	46	69	88	...	3.1	2.9	2.8	3.0	...	140	140	140	144	...
Mean	1.7	1.8	1.5	2.5	1.6	153	161	94	139	102	38	37	33	56	43	3.1	3.1	3.2	3.3	3.1	141	141	142	143	145
Per cent of Control		106	88	147	94		105	61	91	67		97	87	147	113		100	103	106	100		100	101	101	103
P Value <		NS	NS	NS	NS		NS	.20	NS	.20		NS	NS	NS	NS		NS	NS	.30	NS		NS	.30	.10	.20

See Table 1A for key to abbreviations.

TABLE 2.—EFFECT OF PENTOLINIUM ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION IN DOGS ON WHICH CONCURRENT ESTIMATIONS OF MAXIMUM TUBULAR FUNCTION (T_{mG}) WERE MADE

TABLE 2.—EFFECT OF PENTOLINIUM ON RENAL HEMODYNAMICS AND WATER AND ELECTROLYTE EXCRETION IN DOGS ON WHICH CONCURRENT ESTIMATIONS OF MAXIMUM TUBULAR FUNCTION (TmG) WERE MADE

	Mean Blood Pressure mm./Hg				*Renal Blood Flow ml./min.*				*Renal Vascular Resistance**				*TmG†*			*GFR/TmG*			*Dose-Pentolinium mg./kg.*
Dog No.	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	*C*	D_1	D_2	
1.	150	92	102	133	238	243	202	141	.63	.38	.50	.94	116	115	107	.37	.36	.35	2
2.	129	81	86	119	252	255	243	175	.51	.32	.35	.68	131	107	101	.36	.41	.40	2
3.	106	79	100	138	364	311	203	167	.29	.25	.49	.83	140	126	104	.42	.40	.41	2
4.	129	89	67	81	398	358	191	204	.32	.25	.35	.40	199	154	120	.35	.29	.25	2
5.	130	100	110	105	331	324	264	204	.39	.31	.42	.51	119	107	103	.44	.34	.35	2
6.	123	91	109	141	175	154	104	64	.70	.59	1.05	2.20	73	66	65	.41	.41	.40	2
7.	170	91	112	...	431	318	210	...	.39	.29	.53	...	147	150	115	.44	.32	.37	2
8.	144	143	158	...	330	278	279	...	.44	.51	.57	...	188	181	195	.35	.36	.35	2
Mean	135	96	106	120	315	280	212	159	.46	.36	.53	.93	139	126	114	.39	.36	.36	
Per cent of control		71	79	89		89	67	50		78	115	202		91	82		92	92	
P Value <		.01	.05	NS		.05	.01	.01		.001	.01	.10		.05	.05		.20	.20	

	Glomerular Filtration Rate ml./min.				*Urine Volume ml./min.*				*Sodium Excretion μEq./min.*				*Potassium Excretion μEq./min.*				*Plasma Sodium mEq./L.*			
Dog No.	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3	*C*	D_1	D_2	D_3
1.	43	41	37	30	4.0	4.5	5.2	5.9	138	178	147	149	29	31	35	36	133	133	131	130
2.	47	44	40	31	2.6	2.2	4.2	5.1	36	84	88	92	28	41	38	32	135	135	135	135
3.	59	51	43	36	4.6	3.1	2.6	5.2	95	43	28	64	26	25	17	36	143	143	143	140
4.	69	45	30	45	9.8	4.7	4.1	1.4	77	8	3	6	51	32	18	23	138	136	136	136
5.	52	36	36	41	3.5	2.6	3.9	0.8	72	14	25	13	12	15	22	13	127	127	123	130
6.	30	27	26	18	3.5	3.5	4.9	5.7	85	66	147	168	10	10	13	17	130	130	130	130
7.	64	48	42	...	13.1	5.8	6.4	...	564	210	244	...	72	47	38	...	128	127	127	...
8.	65	65	69	...	8.8	6.5	7.0	...	266	157	185	...	50	60	77	...	133	140	138	...
Mean	54	45	40	34	6.2	4.1	4.8	4.0	167	95	108	82	35	33	32	26	133	134	133	134
Per cent of control		83	74	63		66	77	65		57	65	49		94	91	74		101	100	101
P Value <		.05	.05	.01		.10	.30	NS		.20	.30	NS		NS	NS	NS		NS	NS	NS

Key to abbreviations: † = Maximum tubular reabsorption of glucose in mg. minute

* = RVR = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

NS = P Value > 0.30
C = Control, average of three 10-minute periods
D_1 = Immediate post drug period, two 10-minute periods
D_2 = Observations one hour after drug administration
D_3 = Observations two hours after drug administration

in mean blood pressure within 20 minutes after the administration of pentolinium ($p<.001$), the average for the group decreasing from 130 mm. Hg to 98 mm. Hg. The mean blood pressure remained depressed in most of the dogs for at least 2 hours following the administration of pentolinium. However, in some of the animals it had returned to control levels by this time. When observations were repeated 3 days later, the average mean blood pressure had returned to the control levels.

Associated with the reduction in mean blood pressure, there was a slight reduction in glomerular filtration rate from 52 ml. per minute to 45 ml. per minute ($p<.001$), immediately after the administration of the drug and to 38 ml. per minute 2 hours later. This represented a 27% reduction in glomerular filtration rate. There was a parallel reduction in renal blood flow due to a combination of reduced renal plasma flow and a decrease in the hematocrit. There was a significant reduction in renal vascular resistance but this was not great enough to prevent a decrease in renal blood flow. Although the reductions in renal functions were not great, they were consistent enough to be statistically significant ($p<0.05$)*. After 3 days, glomerular filtration rate and renal blood flow had returned to control levels.

The effect of blood pressure reduction with pentolinium on water and electrolyte excretion is summarized in Table 1B. Despite the reduction in glomerular filtration rate, there was not a consistent effect on urine volume or on the excretion rates of sodium and potassium.

Eight dogs were studied in which maximum tubular function (TmG) was determined (Group 2) in addition to the observations made on the dogs in Group 1. These dogs were studied separately since it was thought that high levels of blood glucose might alter the blood pressure and renal response to ganglionic blockade. This did not prove to be the case. The observations on blood pressure and renal hemodynamic responses in this group of dogs were quite similar to those made on the dogs in Group 1. In addition, as the glomerular filtration rate decreased, maximum tubular function decreased slightly but consistently enough to be significant ($p<0.05$). The GFR/TmG ratio was not altered significantly.

Discussion. Any alteration in renal blood flow occurring after the administration of pentolinium would depend on two factors, namely, renal vascular resistance and mean blood pressure. As the blood pressure was reduced, there was a definite reduction in renal vascular resistance; however, this reduction was apparently not great enough to prevent some decrease in renal blood flow. These results are quite similar to observations made after the administration of hexamethonium[3]. It appears that ganglionic blockade of the renal nerves was not enough to produce adequate renal vasodilatation to compensate for the reduction in blood pressure and as a result, renal blood flow and glomerular filtration rate decreased. In contrast, when adrenergic blockade was produced[2] by the administration of phenoxybenzamine (Dibenzyline), a reduction in renal blood flow and glomerular filtration rate did not occur. Apparently, adrenergic blockade and renal vasodilatation were adequate to prevent a reduction in renal blood flow under these circumstances.

Summary and Conclusions. The effect of pentolinium on renal hemodynamics and the excretion rates of water

*A p value less than 0.05 is considered to be statistically significant.

and electrolytes was studied in 18 dogs. Associated with the reduction in mean blood pressure, there was a small but consistent reduction in glomerular filtration rate and renal blood flow. There was no effect on water and electrolyte excretion. Three days after the administration of pentolinium, renal hemodynamics returned to control levels indicating that the acute response was physiological rather than being secondary to renal damage.

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SUMMARIO IN INTERLINGUA

Responsa Renal a Pentolinium: Observationes Laboratorial

Esseva studiate in 18 canes le effecto de pentolinium super le hemodynamica renal e super le excretion de aqua e del electrolytos. Associate con le reduction del pression sanguinee median, il occurreva un parve sed regular reduction in le valores del filtration glomerular e del fluxo de sanguine renal. Nulle effecto esseva notate in le excretion de aqua e del electrolytos. Tres dies post le administration de pentolinium, le hemodynamica renal retornava a nivellos de controlo. Isto indicava que le responsa acute esseva physiologic e non secundari a un lesion renal.

SUMMARIO IN INTERLINGUA

(See page 125 for original article)

Valor e Signification Clinic del Unipolar Derivation Dextero-Bracial in Hypertension

1. Le unipolar derivationes dextero-bracial e thoracic V_6 esseva usate systematicamente pro studiar le potentiales de superficie endo- e epicardial del pariete anterolateral del ventriculo sinistre in casos normal, in casos hypertensive, e in casos de bloco de branca.

2. Definite correlationes poteva esser establite inter le aspectos electrocardiographic de derivationes VR e V_6. Le directiones del unda T in iste derivationes es opponite le un al altere. In casos de normal activation del pariete sinistroventricular, in le stadios initial de hypertension, e in casos de bloco de branca dextere, T_{VR} es negative e T_6 es positive, durante que in stadios avantiate de hypertension e in casos de bloco de branca sinistre, T_{VR} es positive e T_6 es negative.

3. In casos de hypertension, 5 differente configurationes esseva establite secundo le conducta del derivation VR. Cata configuration esseva correlationate con pertinente datos clinic, dimensiones roentgenologic del corde, position del axe electric, e le correspondente indice de effortio. Le configuration VR exhibiva un directe correlation con le severitate del damno myocardial causate per hypertension. Configurationes 1 e 2 indicava stadios initial del affection myocardial; configurationes 4 e 5 indicava stadios avantiate de illo.

4. Le unipolar derivation dextero-bracial per se, e specialmente in combination con le derivation thoracic V_6, provide utile informationes relative al condition del myocardio sinistroventricular in casos de hypertension.

TREATMENT OF THE AMBULATORY HYPERTENSIVE PATIENT WITH PENTOLINIUM TARTRATE

A METHOD FOR REGULATING DOSAGE

By Samuel Waldman, M.D.

ATTENDING PHYSICIAN, UNITY HOSPITAL; ATTENDING CARDIOLOGIST, DEPARTMENT OF MEDICINE, CARDIAC CLINIC, LONG ISLAND COLLEGE HOSPITAL, BROOKLYN, NEW YORK

AND

Louis Pelner, M.D.

ATTENDING PHYSICIAN, SWEDISH HOSPITAL, BROOKLYN, NEW YORK

In our experience, pentolinium tartrate has proved to be a satisfactory drug for the reduction of blood pressure in patients who have severe or moderately severe forms of this disease. Meticulous adjustment of the dosage is the most important single step in this form of therapy. The patient must be made a partner in the therapeutic trial. To achieve success, the patient cannot discontinue the medication because of minor, evanescent side actions. Obviously, this is not a drug to be used in "faint-hearted" patients or for indiscriminate or "casual" prescribing. Nevertheless, extreme care in the adjustment of the dosage of pentolinium will reward the patient with a satisfactory reduction of blood pressure, without excluding the patient from his daily chores. This communication will deal largely with our method of initiating and regulating the dosage of pentolinium tartrate in order to achieve useful reduction of the blood pressure, with minimal side-effects.

With the advent of each new drug proposed for the treatment of hypertension, it becomes essential to obtain new data on the choice of patients, the action and the side-effects of the drugs, the dose, method and time of administration and the prognostic implications. Basic physical and physiological principles must be combined in a practical sense.

Material and Methods. It has been adequately demonstrated that the use of ganglion blocking agents is properly reserved for the more severe instances of hypertension as well as for malignant hypertension. Mild and labile forms of hypertension have shown satisfactory responses to the various sedatives, rauwolfia, veratrum and hydralazine preparations. Since pentolinium, a ganglion-blocking agent, offers a more predictable, more definite, and more prolonged effect on blood pressures than hexamethonium, 26 suitable patients were started on therapy with the drug. We selected patients with diastolic pressures of at least 110 mm. Hg, who had not responded to sedatives, rauwolfia and veratrum preparations as candidates for this therapy. This group included patients in the malignant phase of hypertension and those with evident progressive hypertensive disease as indicated by increasing damage in the heart, kidney or brain. Excluded were elderly patients with systolic hypertension due to arteriosclerosis, since this type is considered a secondary manifestation of arterial rigidity. Systolic hypertension due to aortic insufficiency, hyperthyroidism, and atrio-ventricular block were also excluded since the tension here represents a manifestation of increased cardiac output.

Thirty per cent of the 26 patients were treated with pentolinium for from 3 weeks to 5 months, and 70% received the drug for 6 to 11 months.

CURRENT METHODS OF DETERMINING THE DOSAGE OF PENTOLINIUM. Smirk[13,14]

has advocated both an objective and a subjective procedure for determining dosage of the drug. His ideal method is to check the patient's blood pressure every ½ hour throughout the day, in the standing position until the lowest blood pressure in this position is attained (so-called trough blood pressure). The ideal is felt to be around 120/80, except in patients with angina where the pressure should not be lowered below 140/90, at least at the outset. At this level, one is apt to encounter symptoms of hypotension.

When this procedure is found to be impractical, it is advised that the patient note the doses that cause faintness when in the upright position, and to decrease the doses by one or more increments below this level for maintenance. In other words, Smirk feels that the dose should be just short of that causing postural hypotensive disturbances.

In our series, we noted that although we might reach hypotensive levels in some patients, this could not be constantly maintained. In addition, these same patients frequently had postural hypotension and faintness at much higher levels than expected. For example, one patient with a pressure of 270/140 developed faintness at a level of 180/110 and could not be comfortably maintained at that level. For each patient, the lowest pressure, therefore, consistent with comfort and relief of symptoms is the goal to be attained and maintained. These levels may not be normotensive or hypotensive but indeed may still be at hypertensive levels. Each patient then becomes his own control. By studying the time-pressure curves of patients, it was noted that the hypotensive effect of pentolinium followed a curve with its nadir about 2 to 3 hours following the ingestion of the drug and a more gradual rise for the next 4 to 5 hours, giving a total duration of action of 6 to 8 hours, findings also noted by other investigators[9]. It resembles the blood

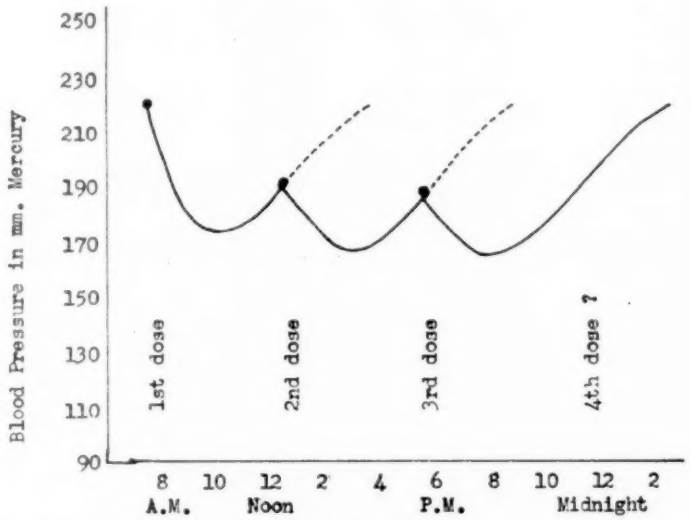

Fig. 1.—Average representative figure of the action of pentolinium administered in three doses by the method described.

sugar curve following the administration of regular insulin, see Fig. 1.

We feel that the blood pressure of a patient should be lowered gradually and not to too low a level. A gradual fall and rise is less apt to cause damage than a sharp fall and subsequent rise, the latter acting as a water hammer type of pressure-bounce, which by its great change in force might cause catastrophic vascular accidents.

Freis[5] has advocated home blood pressure recordings to avoid the stress effect of the physician's presence. This procedure was calculated to avoid overdosage with the drug, which might follow readings under conditions prone to cause undue elevations. He noted the majority of home readings to be substantially lower than office readings.

THE RATIONALE OF OUR METHOD IN DETERMINING THE DOSAGE OF PENTOLINIUM. Normally, the systolic and diastolic blood pressures are higher in the sitting posture and lower in recumbency. This is related to a normal reflex compensatory mechanism subject to gravity effect, which assures an adequate blood flow to the cerebral vessels. Nervous mechanisms which regulate the caliber of arterioles, especially in the splanchnic area, are called into play to counteract this gravity effect, by reflex vasoconstriction. In upright positions, the systolic rises to a lesser extent than the diastolic so that the pulse pressure becomes narrower. In recumbency, the diastolic falls more than the systolic, so that the pulse pressure rises. The diastolic pressure invariably falls in recumbency and rises in the upright station. The systolic pressure may, however, in regularly hypotensive persons, rise when lying down and fall in the erect posture[3].

When patients are given a sufficient dose of pentolinium, the above described reflex is blocked. Compensatory vasoconstriction is prevented while under the influence of the drug and at this time it was observed that patients exhibited higher brachial pressures in recumbency and lower pressures when in the sitting position. This can be likened to gravitational flow in a rigid, inelastic tube with rapid vertical downflow unhindered, compared with a slower flow in more horizontal positions. On reclining the gravitational effect is diminished. This phenomenon is opposite to the normal reflex mechanism which causes blood pressure to rise in the sitting position and fall when recumbent. This observation has been utilized in the calibration and regulation of the doses of pentolinium that we used.

We took the blood pressure readings as a control study on 100 unselected normal and hypertensive (not treated with blocking agents) patients. It was found that 85% had higher pressures, both systolic and diastolic, when seated than when recumbent and 10% had substantially no change when recumbent. Five per cent showed a slight elevation in recumbency. These were patients whose pressures were normally at lower levels. Patients who had taken or were still taking reserpine or veratrum drugs also showed elevated pressures when seated and lower pressures when recumbent, as occurs in the normal state.

Utilizing these physiologic and clinical facts, we administered pentolinium aiming to break the postural vasoconstrictor reflex and to use this as our guide. If the reflex were broken, the pressure would fall on sitting up and rise on reclining. This would indicate that the drug was effective and should either be very cautiously increased in dosage or it should not be increased at all, depending upon the level of pressure attained. If the reflex was unbroken, then the dose could be increased

without hesitation. Five various combination possibilities have evolved from this method and these are noted in Fig. 2 which we used as our guide in the administration of pentolinium.

It is important to remember that when pentolinium is administered in effective dosage, the blood pressure taken in seated and reclining postures will indicate whether the vasoconstrictor postural reflex is intact or broken. This holds true independent of the time the pressure reading is taken provided it is during the time the drug is active, which is generally up to 8 hours after ingestion.

TREATMENT OF PATIENTS WITH SEVERE OR MODERATELY SEVERE HYPERTENSION

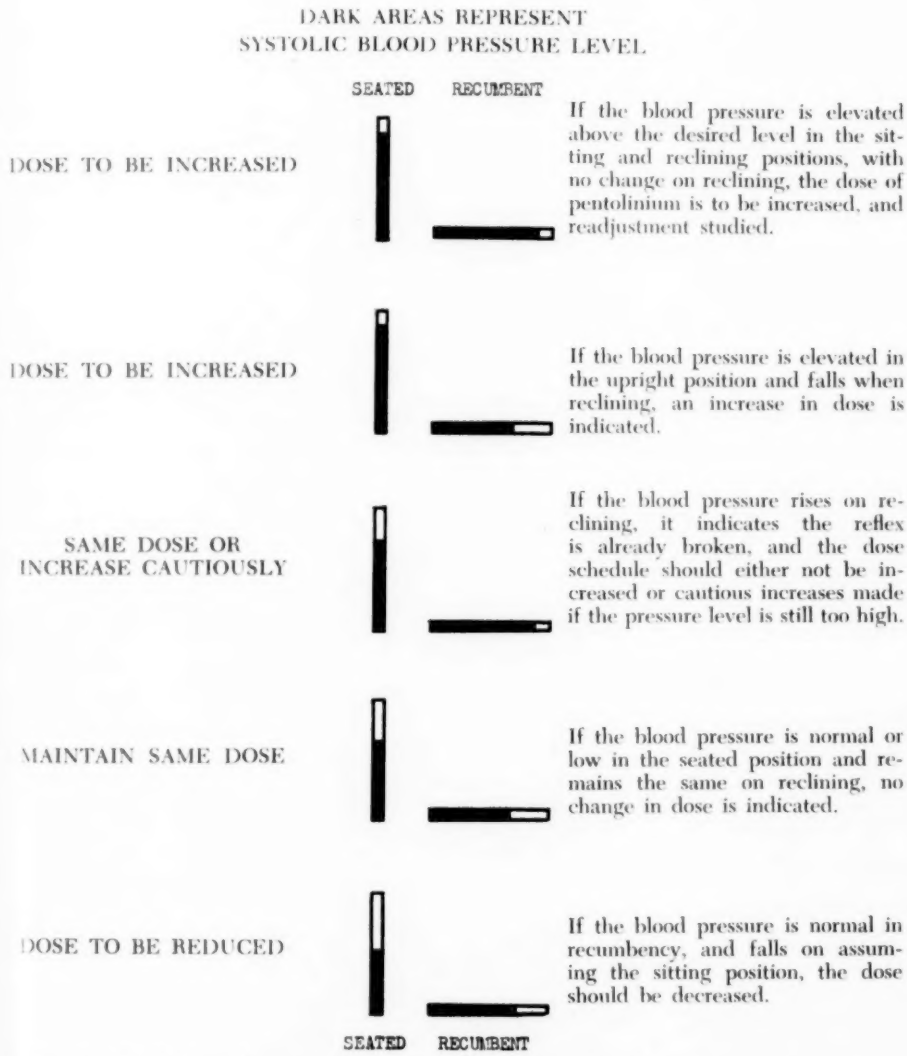
DARK AREAS REPRESENT
SYSTOLIC BLOOD PRESSURE LEVEL
SEATED
RECUMBENT
DOSE TO BE INCREASED
If the blood pressure is elevated above the desired level in the sitting and reclining positions, with no change on reclining, the dose of pentolinium is to be increased, and readjustment studied.
DOSE TO BE INCREASED
If the blood pressure is elevated in the upright position and falls when reclining, an increase in dose is indicated.
SAME DOSE OR INCREASE CAUTIOUSLY
If the blood pressure rises on reclining, it indicates the reflex is already broken, and the dose schedule should either not be increased or cautious increases made if the pressure level is still too high.
MAINTAIN SAME DOSE
If the blood pressure is normal or low in the seated position and remains the same on reclining, no change in dose is indicated.
DOSE TO BE REDUCED
If the blood pressure is normal in recumbency, and falls on assuming the sitting position, the dose should be decreased.
SEATED
RECUMBENT

Fig. 2.—Guide chart for the administration and adjustment of dosage of pentolinium.

WITH PENTOLINIUM. Before starting treatment, the patient's pressure is recorded in the sitting and recumbent positions. The patients are seated on the examining table and the blood pressure cuff is applied and readings taken. The patient is then left alone for about 10 minutes. The pressures are then taken again. In this short interval a fall in pressure will be noted which will be about equivalent to a basal reading.

These figures were noted on our records as the "angle method" of recording, thus:

$$\text{B.P.} \begin{cases} 180/100 \\ \diagup \\ 170/90 \end{cases} \qquad \text{See Fig. 3.}$$

The horizontal line represents the recumbent pressure readings, while the oblique line represents the seated readings.

Throughout this paper, the blood pressure readings are read as B.P. (S) seated and B.P. (R) recumbent or diagrammatically as

$$260/120 \text{ (S)eated}$$
$$\diagup$$
$$256 \text{ (R)ecumbent.} \quad \text{See Fig. 3.}$$
$$112$$

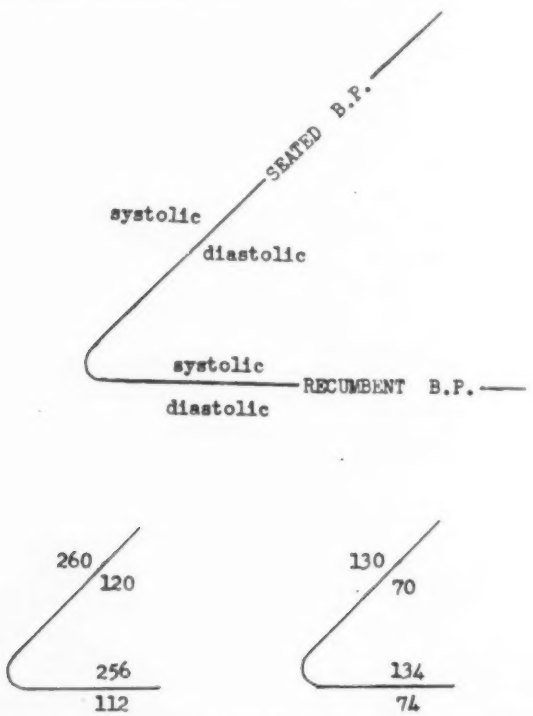

Fig. 3.—Angle method of recording the systolic and diastolic, seated and recumbent blood pressure readings on the patient's record, while under treatment with pentolinium.

After having originally used doses of 40 to 100 mg., we noted such untoward side-effects due to too rapid and precipitous drops in pressure, that we feel, as do Ashby and associates[2], that initial doses should be low.

The pentolinium was administered therefore initially as 10 mg. or 20 mg. three times daily, *one-half hour before meals* and recorded in our table as

20-20-20 on a three-dose basis. The smaller dose was used in apprehensive patients or where we felt full cooperation might be lacking. We noted that the drug had a lesser effect when given with or after meals. Since uncompensated splanchnic dilatation contributes to the fall in pressure, it became apparent that a potentiating effect was obtained especially 2 to 2½ hours after meals, which with the added ½ hour before meals resulted in a maximum effect for the specific dose.

ment the pressure is greater in the reclining position, it is advisable in severe cases, especially those who awaken with headaches, to give an additional dose at bedtime to potentiate the evening dose and help maintain a lower pressure during sleeping hours. Smirk[14] has advocated a bed posture of 45 degrees to derive this positional benefit. When increasing the dose from the 20-20-20 schedule, the first dose to be augmented should be the evening dose, then the morning dose and lastly the

TABLE 1.—ADJUSTED DOSAGE OF PENTOLINIUM

No. Patients	*Mg. in Daily Dose Schedule*
3	60 — 60 — 60
3	50 — 50 — 50
2	100 — 100 — 100
2	20 — 20 — 20
1	100 — 50 — 150
1	80 — 80 — 80
1	70 — 60 — 100
1	70 — 60 — 90
1	70 — 70 — 70
1	70 — 60 — 70
1	50 — 40 — 50
1	50 — 30 — 70
1	50 — 30 — 50
1	40 — 40 — 60
1	40 — 40 — 40
1	40 — 20 — 40
1	30 — 30 — 30
1	20 — 20 — 40
1	20 — 0 — 40
1	10 — 0 — 40
26	

Doses of the drug were increased or decreased according to diagram, in increments of 10 to 20 mg. per dose. All symptoms were carefully recorded between visits and adjustments or supplementary medication advised (*vide infra*). Bouncing pressures were avoided as previously explained. The pressures were recorded in time relationship both as to food and medication. Most readings were taken 2 to 3 hours after medication and occasionally just prior to the next dose so that troughs and peak levels were often obtainable. Since in patients under treatmidday dose, since the latter has an additive effect on the morning dose. Sudden interruption of all doses should be avoided to prevent a precipitous, dangerous rise in pressure. The maintenance doses of pentolinium arrived at in our series of 26 patients are summarized in Table 1.

The addition of reserpine routinely in a dose of 0.25 mg. three times a day, after meals was found to enhance the effect of pentolinium[7,13], permitting the use of smaller doses with a resultant decrease in side-effects and earlier appearance of symptomatic re-

lief. Since reserpine action has a latent period of 1 to 2 hours[11], its administration after meals permits its effect to coincide with the peak of action of pentolinium. Its use also diminishes the constipating effect of pentolinium, due to its augmentation of motor activity of the gastrointestinal tract[11]. In our experience the use of reserpine is practically essential to the proper and comfortable administration of pentolinium.

SIDE-EFFECTS. Some side-effects are inevitable with a drug such as pentolinium. The objective in our treatment should be the satisfactory reduction of blood pressure, with minimal side-effects. With meticulous prescribing, this goal can be attained.

Pentolinium is a potent, autonomic ganglionic blocking agent, and while both parasympathetic and sympathetic ganglia are blocked to some extent, the main effect is against the sympathetic ganglia. We thus find various side-effects such as postural hypotension, dryness of the mouth, blurred vision, constipation and occasional impotence in the male, especially in the older patients. These uncomfortable side-effects can also be used to help determine dose schedule and administration.

Constipation was noted by most patients by the end of the first week. Milk of magnesia given daily avoided this in the majority of instances. Where this failed, oral neostigmin was almost always effective in a 15 mg. dose taken in the morning. Occasionally this dose caused diarrhea and necessitated a reduction in the dose to 7.5 mg. in the morning. No instances of ileus were noted. It is essential in the program of therapy to insist that the patient have a bowel movement every day in order to avoid the absorption of drug accumulated in the bowel which might cause precipitous hypotension. With the regular use of reserpine, less constipation was noted.

Postural faintness was more frequent in the earlier days of the investigation. With careful administration and patient education, this symptom became inconsequential and easily overcome by reclining when such symptoms arose. Women were advised to slip into their abdominal supports while in bed, and in this way frequently avoided morning postural hypotension, which was the most frequent time of this episode. Its time relationship to the ingestion of pentolinium was usually 2 hours *post tabellam*. Blurred vision due to paralysis of accommodation was not a disturbing side-effect in our series.

Dryness of the mouth, which was an annoying symptom early in treatment later cleared spontaneously. Impotence occasionally appeared with treatment but when not initially present, was detected only by close questioning. No urinary disturbances were noted.

Proper treatment requires intelligent cooperative patients, who are anxious to help themselves, and who must be taught the reactions to be anticipated. Fearful patients, who tremble at the thought of postural hypotensive symptoms, will not cooperate and will fail to persist in the course of treatment.

AUGMENTING FACTORS. Potentiation of the action of pentolinium is noted following the ingestion of alcohol, after exercise, salt depletion, after meals, following a hemorrhage, and during exposure to heat or hot weather. Freis[7] found it necessary to reduce the dosage of pentolinium when giving mercurial diuretics. In noncardiacs, a moderate salt intake was permitted since marked restriction of sodium caused exaggerated hypotension responses, in some individuals. We did not find rigid restriction of salt necessary with the use of pentolinium, as has also been noted by other observers. Dosages should be

reduced when augmenting factors are anticipated, such as in hot weather, (with vasodilatation and loss of salt due to excessive perspiration), during alcohol excesses and with the use of mercurial diuretics.

Of the 26 patients treated, one illustrative case is presented in detail. An account of the entire series will be reported subsequently.

Case Report. F.E., a 46-year-old female, was first seen on November 2, 1954, with a history of hypertension for the preceding 5 years. The onset followed a hysterectomy. She complained, when seen, of severe frontal and occipital headaches, visual blurring, irritability, and emotional instability. The patient had been under medical care at several hospitals and clinics. She narrated a list of treatments with reserpine, hydralazine, and hexamethonium. Despite all therapy, symptoms persisted as well as blood pressure, with levels of 260 to 280 mm. Hg systolic and 110 to 160 mm. Hg diastolic.

Examination revealed an apprehensive female weighing 120 lbs. The blood pressure was 260/120 (S),

256 (R)
112

which is read as B.P. (S) seated, 260/120 B.P. (R) recumbent, 256/112 (see Fig. 3). The ocular fundi showed a grade IV papillitis with blurred disc margins. Red and white patches were noted in the left fundus. The neck was not rigid. The heart exhibited a grade 3 systolic murmur at the apex, and a grade 2 systolic aortic murmur. A_2 was greater than P_2 and was sharp and snapping. The lungs were clear. Palpation of the abdomen disclosed a liver edge 4 cm. below the costal margin. No peripheral edema was present.

Fluoroscopy revealed rounding of the left ventricle and prominent aortic pulsations. The urine showed a 2 plus albuminuria. Blood urea N was 19 mg. per 100 ml. of blood.

The electrocardiogram showed a pattern of marked left ventricular strain. (See Fig. 4.)

This patient was initially given 40 mg. of pentolinium 3 times daily ½ hour before meals. Bowel hygiene was discussed since the patient was ordinarily constipated. Neostigmin hydrobromide, 15 mg., was given in the morning. The patient noted weakness and faintness when up and around, and 5 days later, 3 hours *p.t.* (*post tabellam*, after taking the tablet), she collapsed. When seen, her pressure was 140/80 (S) and 230/120 (R). Lying in bed relieved the faintness almost immediately. In view of the pressure findings and the obvious blocking of the vasoconstrictor reflex, the dose was reduced to 20 mg. three times a day. Three days later the pressure 3 hours *post tabellam* was 180/100 (S), 220/100 (R). At this time, reserpine 0.25 mg. was added to the regimen, three times daily, after meals, to help avoid the marked pressure fluctuations. Neostigmin, because of diarrhea, was reduced to 7.5 mg. in the morning with smooth and more comfortable action. Five days later, the patient still complained of faintness 3 hours *post tabellam* but at 7 hours *p.t.* felt very comfortable. At this time the pressure was 190/90 (S) and 190/90 (R). There was no headache, vertigo or faintness. Since faintness was most prominent in the morning, the patient was advised to wear a corset on awakening and adjust her dose to 20-0-40 (20 mg. ½ hour before breakfast, none before lunch, 40 mg. ½ hour before dinner) and to take reserpine 0.25 mg. after meals. One week later the patient stated that she had not felt so well in years. There was no faintness and the vision improved. The blood pressure 2 hours *p.t.* was 140/80 (S) and 190/90 (R) indicating the action of pentolinium was still evident and no change in dose necessary. In January, 1955, the fundi showed clear disc margins and no hemorrhage, recent or old. The arteries still showed tortuosity. In February, 1955, after 4 months of therapy, the electrocardiogram showed a diminution in T wave changes in the precordial leads. (See Fig. 4.) The chest roentgenogram showed less enlargement of the left ventricle with a cardio thoracic ratio of 13.2 cm./27.6 cm. The urine showed no albumin and the microscopic study was negative. The blood urea nitrogen was 12.5 mg., creatinine 1.0 mg., and the uric acid 3.1 mg. per 100 ml. of blood.

After 8 months of treatment, the patient feels very well, has no complaints, is on a dosage schedule of 20-0-40 of pentolinium and takes 0.25 mg. of reserpine after meals. Her last blood pressure was, 6 hours *p.t.* 130/70 (S), 134/74 (R). See Fig. 3.

Discussion. In a recent editorial, Schroeder[12] debated the question, "Why not control hypertension with drugs?" The only cautions advised

were to avoid rapid lowering of pressure in patients with azotemia and in atherosclerosis of the cerebral and coronary arteries. Angina was relieved in 9 of 10 cases with associated hypertension. Cautious application of treatment is strongly urged. Freis[6] states that in a patient with a nonprotein nitrogen above 100 mg. per 100 ml., hypotensive therapy will do more harm than good. Similarly, Fishberg[4] finds that lowering blood pressure by powerful antipressor drugs may cause ischemic changes in the heart or brain, if a high degree of arteriosclerosis is present. Myocardial or cerebral infarction may result and even prove fatal. Insofar as some instances of cerebral hemorrhage occur where there are spotty, focal, sclerotic changes, the use of these drugs may be undertaken cautiously. Smirk[13,14], although recognizing the valid consideration of a compensatory circulatory loss of flow during pressure

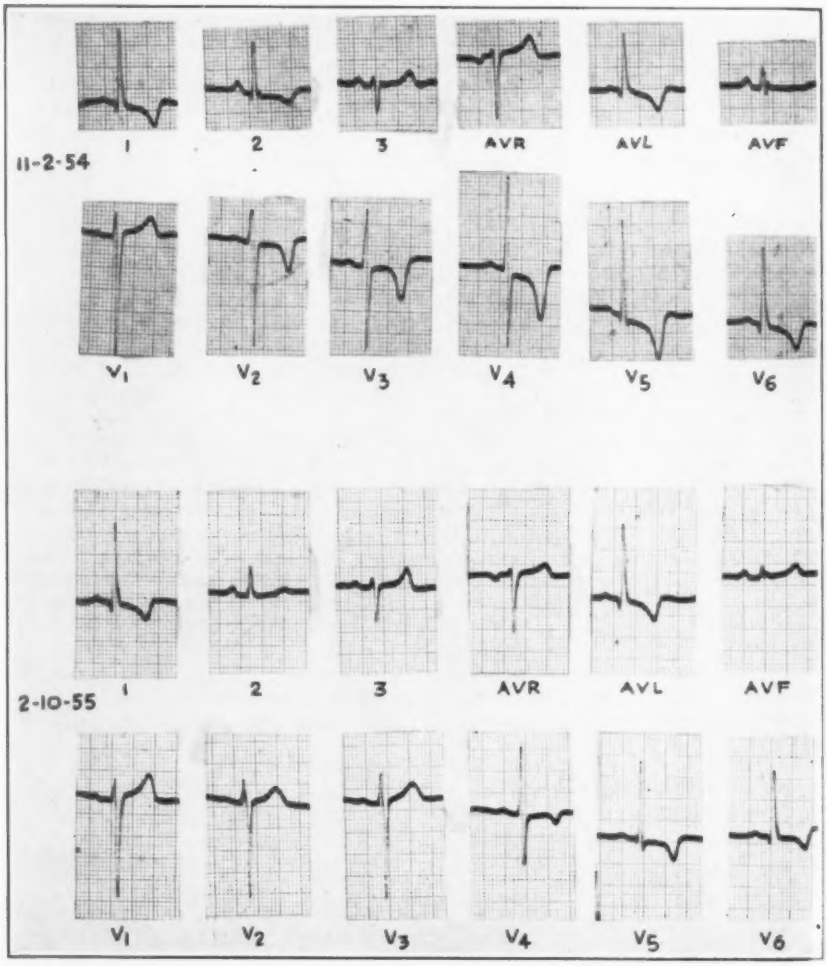

Fig. 4.—F.E., female, aged 46. Electrocardiograms taken on Nov. 2, 1954, and again on Feb. 10, 1955, while on pentolinium therapy.

reduction in patients with an already diminished blood flow in the heart, brain and kidneys, feels that treatment should not be withheld. However, he proposes a 6-week waiting period following a cerebral or coronary thrombosis. Smirk also suggests more conservative hypotensive attainment in individuals with angina pectoris.

The studies of Persson[10] are in line with our impression of the use of ganglion blocking agents in the treatment of hypertension. He studied the effect of pentolinium in a series of 15 patients, with evidence of arteriosclerosis, whose average age was 64 years. Nine patients had symptoms of cerebral thrombosis over 3 months prior to study. He found these patients felt best when their pressures were about 180/105, seated. The effective dose avoided side-effects. A greater fall in pressure or a too rapid fall caused dizziness, pallor, tachycardia and perspiration which failed to subside immediately on reclining. His investigation leads him to conclude that a careful dosage adjustment without too much concern for marked fall in pressure, may still produce a significant improvement subjectively and objectively.

Similarly, Kleh and his co-workers[8], in a recent study, noted that the use of agents which blocked postural vasoconstrictor reflexes was hazardous in patients with hypertensive cerebral vascular disease. This indicates the necessity for extreme care in dealing with this type of patient.

It is apparent that the use of blood pressure reducing agents in severe cases is indicated primarily for the comfortable relief of symptoms without drastic reduction in pressure, which might cause intolerable side-effects. A moderate reduction in blood pressure is frequently consistent with the well being of the patient. Marked reduction caused such discomfort that it could not be tolerated. Weakness, faintness, dizziness, undue fatigue and drowsiness might ensue. Following subjective relief, which can be attained by cautious, gradual and meticulous dosage adjustment, objective relief is almost certain to follow.

In our series of cases, the average reduction in blood pressure was:

Seated (S) systolic, 61 mm. Hg; diastolic, 32 mm. Hg

Recumbent (R) systolic, 47 mm. Hg; diastolic, 23 mm. Hg.

Improvement in retinal changes were similar to the findings of Smirk; papillitis, papilledema and hemorrhages disappeared. The anginal syndrome disappeared or became milder in 3 of 4 patients.

Five patients with congestive failure, at the initiation of treatment were controlled without further episodes.

Patients with diabetes showed no change in this condition.

Urea nitrogen in all patients where it was normal at the start remained normal. In 2 patients, with nitrogen retention a decrease was evident as the condition improved.

The largest dose of pentolinium used by us was 300 mg. per day, which was lower than previously reported dosages.

Agrest and Hoobler[1] using much larger daily doses (up to 600 mg. per day) noted, in a study of 31 patients, normalization of the mean standing blood pressure in 31% and a reduction of pressure of more than 20 mm. Hg in 87%. The median reduction was 38 mm. Hg. In recumbency, one patient reached normal levels. Sixty-eight per cent dropped 20 mm. Hg or more and the median reduction was 23 mm. Hg. We did not seek falls to normotensive levels. Our method of regulating the dosage of pentolinium was also useful with other blocking agents.

Summary. Pentolinium tartrate proved highly satisfactory for reduction of blood pressure in 26 patients with severe or progressive hypertension during treatment periods varying from 3 weeks to 11 months.

The drug was administered orally three times daily for a total dose of not more than 300 mg., all doses being given one-half hour before meals. Reserpine, 0.25 mg., was administered immediately after meals. In all patients, significant falls (not necessarily to normal levels) occurred in systolic and diastolic blood pressure, in both the seated and recumbent positions.

The cardiac, retinal and coronary status of all patients was improved, whether or not the blood pressure was reduced to levels approaching normal. One patient died of cerebral hemorrhage, despite a fall in pressure of 36 mm. Hg systolic, and 38 mm. Hg diastolic.

With proper regulation of the treatment schedule, side-effects were controlled.

Meticulous adjustment of dosage is the most important single step in the use of pentolinium. The physiologic ganglion-blocking action of pentolinium in interrupting the normal compensatory vasoconstrictor reflex, which comes into play by postural variations, was used as a guide to determination of the most suitable dose for the individual.

Blood pressure readings, taken at any time during the activity of the drug (a total of about 8 hours), and recorded by the "angle method," will indicate whether the vasoconstrictor postural reflex has been broken or is still intact; hence whether or not the dose should be adjusted.

ACKNOWLEDGMENT: Supplies of pentolinium (Ansolysen) were generously supplied by Mr. George G. Alperin and Dr. Daniel L. Shaw, Jr., of John Wyeth, Inc., Philadelphia, Pa. Supplies of reserpine (Serpasil) were generously supplied by Mr. Rudolph C. Friedrich and Dr. J. Campbell Howard, Jr., of Ciba, Inc., Summit, N. J.

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(Interlingua on page 176)

COCCIDIOIDES IMMITIS IN THE SOIL OF THE SOUTHERN SAN JOAQUIN VALLEY*

By Roger O. Egeberg, M.D.

and

Ann Frank Ely, M.D.

(From Wadsworth General Hospital, Veterans Administration Center, Los Angeles, California, and the Department of Medicine, University of California Medical Center, Los Angeles, California)

In searching for the nidus of the mycelial phase of *Coccidioides immitis*, one must consider among other possible sites mammals, living and dead, reptiles, vegetation, dung, and the soil itself. In order to throw light on the possible relationship between the animals and the soil and to learn more about the behavior of *Coccidioides immitis* in nature, we began several years ago to trap small mammals, catch reptiles, gather plant life, and collect soil samples in the southwestern part of the San Joaquin Valley.

This paper deals with the percentile recovery of *Coccidioides immitis* from 500 soil samples collected between Buttonwillow and McKittrick.

Experimental Methods. Soil samples were collected in test tubes or jars from the walls of animal burrows and from the open areas between burrows. At each random site, all being five or more feet away from the nearest burrow, four samples were taken: one from the surface, one 4 inches below the surface of the ground, and one each at 8 and 12 inches below the surface. One hundred and seventy-seven burrow samples, 93 random surface samples, 78 samples 4 inches below the surface, 77 samples 8 inches below the surface, and 75 samples 12 inches below the surface were thus collected. Three hundred and eighty of these samples were collected in mid-January, 1954, toward the end of the seven-month dry season. One hundred and twenty were collected in early April, 1955, shortly after the end of the wet season and following several weeks of warm weather.

In the laboratory, the samples were handled as follows: After one minute of shaking of each sample, 1 gm. was removed and suspended in 9 ml. of sterile water in a test tube. From this 1 to 10 dilution, suspensions of 1 to 100 and 1 to 500 were made. (In the case of the larger samples, 10 gm. were removed, suspended, and diluted proportionately.) Plates of Sabouraud's fortified medium were inoculated in duplicate with ½ ml. from each of the 3 dilutions, thus making 6 plates from each soil sample. The plates were allowed to incubate at room temperature from 10 to 20 days and were then examined grossly. All colonies that were suggestive of *Coccidioides immitis* were examined microscopically. Subcultures were made on straight Sabouraud's medium from those colonies whose microscopic morphology was typical of, or similar to, *Coccidioides immitis*. If after suitable incubation they looked typical grossly and microscopically, material from the colony was inoculated into mice for observation of lesions or recovery of spherules, or both, the final proof that the fungus was *Coccidioides immitis*. No cultures were considered positive for *Coccidioides immitis* unless the above criteria were met.

Results. From the first 500 soil samples tested in this analysis, *Coccidioides immitis* was recovered from 35, or 7%. This included random samples and burrow wall samples; and the two major seasons (Table 1).

The distribution of *Coccidioides immitis* in the 500 soils tested was as

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follows: 177 samples from animal burrows yielded 24 positive cultures or 13.6%; 323 random samples from the surface and varying depths yielded 11 positive cultures, or 3.4% (Table 2).

Samples collected in the two major seasons were distributed as follows: 380 were collected in mid-January, 120 in mid-April. In the first group, there were 16 positive samples, or 4.2%. In the second group, there were 19 positive samples, or 16%. In the first group, 137 animal burrows yielded 10 positive cultures, or 7.3%. Two hundred and forty-three random samples from the surface and at 4, 8, and 12 inch depths yielded 6 positive cultures, or 2.5%.

TABLE 1
COCCIDIOIDES IMMITIS IN SOIL

Number of Samples	*Number Positive*	*% Positive*
500	35	7

TABLE 2
COCCIDIOIDES IMMITIS IN SOIL

	Number	*Number Positive*	*% Positive*
From Burrows	177	24	13.6
Random Samples	323	11	3.4

These positive cultures were found primarily below the surface. As opposed to this, the 120 samples taken at the end of the rainy season in April, 1955, gave the following results: 40 animal burrows yielded 14 positives, or 33 1/3%. Eighty random samples taken from the surface and at 4, 8 and 12 inch depths yielded 5 positives, or 6.1%. In this instance, the only positive cultures of the group were on the surface (Table 3).

Discussion. The over-all statistic of 7% positive cultures from 500 soil samples would corroborate the work of Plunkett and Lubarsky, who found approximately 6% of their soil cultures to be positive.

In our series, the striking statistical difference between the positive results found in the samples obtained from the walls of animal burrows and the samples taken at random would seem to point to the animal burrows as offering something environmental that was conducive to the growth or concentration, or both, of *Coccidioides immitis*.

TABLE 3
COCCIDIOIDES IMMITIS IN SOIL

	Number	*Number Positive*	*% Positive*
Collected End of Dry Season	380	16	4.2
Collected End of Wet Season	120	19	16.0

One could postulate many things in this connection, such as protection afforded by burrows from the very high summer surface temperatures, or from short torrential winter rains, or the burrows might act primarily as collecting receptacles for the fungi picked up from the surface of the ground by the burrow tenants' fur. Conceivably, the nitrogen content of the soil at the site of the burrow might be slightly higher and more conducive to growth. Insects associated with the animals could play a part, or organisms carried by the animal might encourage the growth of *Coccidioides immitis*. Whatever the reason, the statistical difference is significant, and we are investigating this further.

A comparison between the results obtained from soils collected at the end of the dry season and those collected at the end of the wet season deserves comment. First, the percentage of positive samples is appreciably higher at the end of the wet season than the dry. Second, the ratio of burrow samples

that gave positive results to random samples that gave positive results in the two seasons is similar if not exactly proportionate, and finally the location of the positive random samples in the two different seasons is interesting. Of the 6 positive random soil samples procured at the end of the dry season, only one came from the surface, the others being from 4, 8, or 12 inch depths. As opposed to this, all of the positive random samples collected at the end of the wet season came from the surface. There were no positive random samples below the surface in this group (Table 4).

TABLE 4.
COCCIDIOIDES IMMITIS IN SOIL

Random Samples
% Positive

	January			*April*		
Source	*No. of Samples*	*No. Pos.*	*%*	*No. of Samples*	*No. Pos.*	*%*
Surface	73	1	1.3	20	5	25
4" Depth	58	2	3.4	20	0	0
8" Depth	57	1	1.7	20	0	0
12" Depth	55	2	3.6	20	0	0

The paucity of positive results on the surface of the ground at the end of the dry season probably indicates the sterilizing effect of the sun's heat which for weeks on end keeps the top centimeter of soil above 125° F. through the 4 or 5 hottest hours of each day. The negative results in the subsurface specimens gathered at the end of the rainy season are more difficult to try to explain.

We should like to suggest a possible explanation for the large percentage of positive surface samples among those collected at the end of the wet season. It is known from the work of Plunkett and Lubarsky, Smith, and others that *Coccidioides immitis* can be grown in sterilized soils with ease, but only with considerable difficulty or careful nursing does it seem to grow in untreated or unsterilized soil. Could it be that this scorching, sterilizing summer heat is necessary to the life of *Coccidioides immitis* in that it prepares a thin layer of relatively sterile soil which needs only moisture to make it susceptible to invasion by the fungi living below and adjacent to it? Could this heat be an ally of *Coccidioides immitis* by giving it, for a brief period of time, a growth medium not thoroughly contaminated with its antagonists and competitors?

Summary. Over 500 soil samples were collected in the southwestern sector of the San Joaquin Valley: from the surface of the ground, at levels 4, 8, and 12 inches below the surface, and from the walls of animal burrows. In the first 500 consecutive samples, *Coccidioides immitis* was recovered from 35. This is 7%.

One hundred and seventy-seven of the 500 samples were collected from burrow walls, and of these 24, or 13.6%, were positive for *Coccidioides immitis*. Of 323 samples collected at random, 11, or 3.4%, were positive for *Coccidioides immitis*.

Three hundred and eighty of the 500 samples were collected at the end of the dry season and of these 16, or

4.2%, were positive for *Coccidioides immitis*. Of 120 samples collected at the end of the wet season, 19, or 16%, were positive for *Coccidioides immitis*. Of the random samples collected at the end of the dry season, all but one of the positive samples came from below the surface. Of the random samples collected at the end of the rainy season, all the positives came from the surface, none from depths. A possible explanation is suggested.

SUMMARIO IN INTERLINGUA

Coccidioides Immitis in le Terra del Sud del Valle San Joaquin

Plus que 500 specimens de terra esseva colligite in le section sud-west del Valle San Joaquin: al superficie, a profunditates de 10, 20, e 30 cm, e ab le parietes de excavationes animal. Inter le prime 500 specimens, *Coccidioides immitis* esseva constatate in 35. Isto es 7 pro cento.

Le 500 specimens includeva 177 colligite ab le parietes de excavationes animal. Inter istos, 24 (o 13,6 pro cento) esseva positive pro *C. immitis*. Inter 323 specimens colligite al hazardo, 11 (o 3,4 pro cento) esseva positive pro *C. immitis*.

Le 500 specimens includeva 380 colligite al fin del periodo aride. Inter istos, 16 (o 4,2 pro cento) esseva positive pro *C. immitis*. Inter 120 specimens colligite al fin del periodo humide, 19 (o 16 pro cento) esseva positive pro *C. immitis*.

Inter le specimens colligite al hazardo al fin del periodo aride, omne le specimens positive con un sol exception esseva subsuperficial. Inter le specimens colligite al hazardo al fin del periodo pluviose, omne le specimens positive sin un sol exception esseva superficial. Un explication possible es proponite.

DIAGNOSTIC SIGNIFICANCE OF CHANGES IN FREE, ESTERIFIED AND PROTEIN-BOUND CHOLESTEROL, LIPO- AND GLYCO-PROTEINS IN LYMPHOMA AND MULTIPLE MYELOMA*

By Sergio I. Magalini, M.D.**
RESEARCH ASSOCIATE, SAINT ELIZABETH'S HOSPITAL

Mario Stefanini, M.D.
DIRECTOR OF RESEARCH AND HEMATOLOGIST, SAINT ELIZABETH'S HOSPITAL;
ASSOCIATE PROFESSOR OF MEDICINE, TUFTS UNIVERSITY, SCHOOL OF MEDICINE;
ESTABLISHED INVESTIGATOR, AMERICAN HEART ASSOCIATION

AND

Hector M. Marin, M.D.
ASSISTANT RESIDENT IN SURGERY, SAINT ELIZABETH'S HOSPITAL

(From the Research Laboratories, Saint Elizabeth's Hospital and the Department of Medicine, Tufts, University School of Medicine, Boston, Massachusetts)

Alterations in the electrophoretic pattern of serum proteins are seen in various hematologic diseases. They are fairly typical in some instances, as in multiple myeloma[1,4,12,17,18]. In others, like in leukemias and lymphomas, electrophoretic changes are less specific but still of value in diagnosis and study of the evolution of the disease[1,14,15,18]. Until lately, investigation has been limited to serum proteins. More recently, equally interesting observations have been published on the electrophoretic migration of lipo- and glycoproteins in multiple myeloma[17].

The present article discusses the extent and diagnostic significance of changes in serum cholesterol level and electrophoretic migration of serum proteins, protein-bound cholesterol, lipoproteins and glycoproteins in some hematologic disorders. Included in this study are 31 patients with various types of lymphoma in different stage of evolution and in clinical remission or relapse, and 4 cases of multiple myeloma. Healthy individuals, before and after fatty meal, and 2 patients with parenchymal liver disease were used as controls. In each case the diagnosis was established through examination of tissue biopsy or postmortem examination.

Methods. *Serum proteins* were determined by Howe's technique[10] and their electrophoretic migration with the method of Durrum[3]. *Electrophoretic migration of lipoproteins* was studied with the method of Durrum *et al.*[5]. After migration, paper strips were stained with oil red[5] and density values read with Photovolt 525† using a 525 λ filter. The quantitative values reported are percentages of total density calculated with a compensating polar planimeter.† *Migration of glycoproteins* was determined with the method of Köiw[11]. Their concentration in each serum protein fraction was expressed qualitatively as + or −, using as means of comparison a similarly treated paper strip of the serum from a fasting, healthy donor. This qualitative technique was used instead of a quantitative one because of the difficulty in direct reading by Photovolt with the ordinarily avail-

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**On leave of absence from the Department of Medicine, University of Rome.

†Photovolt Corp., New York.

able filters. *Total serum cholesterol* was determined by two different techniques. In a preliminary series where serum cholesterol and cholesterol esters were studied in a series of 19 patients with various types of lymphoma, the classical method of Schönheimer and Sperry was employed. In the remaining studies, a modification of the method of Zlatkis[19,20] was followed, determinations being done on the lipid fraction rather than whole untreated serum. Lipid fraction was obtained by extraction from serum with boiling mixture of acetone and absolute alcohol in equal volumes, the residue being dried in desiccator. Results with this technique are closer to those obtained with the Schönheimer-Sperry method than when the original procedure of Zlatkis is used[2]. *Determination of electrophoretic mobility of protein-bound cholesterol* was carried out with a technique developed in this laboratory. A 2" wide Whatmann No. 3 filter paper sheet was divided lengthwise by pencil line in two strips of ¾" and 1¼" respectively. One or two drops of serum flowing from a capillary pipette were applied in each area respectively. Migration of the proteins and of protein-bound cholesterol was obtained following Durrum's technique[3]. After migration, the narrower strip was separated and stained for detection of proteins by Durrum's method[3]. Location of various protein electrophoretic fractions was then established by reading with a model 525 Photovolt using a 595 λ filter. After apposition of the two strips, the unstained larger one was cut transversally to separate the various fractions. The individual sections were then introduced in test tubes and covered with 3 ml. of a mixture of equal volumes of acetone and absolute alcohol. Test tubes were transferred to a water bath at 100° C. until the mixture reached the boiling point, and was then poured into glass-stoppered test tubes. Extraction was repeated once more and the two eluates combined and dried in desiccator overnight. Three milliliters of pure acetic acid were added to the dry residue and the test tubes repeatedly shaken to bring cholesterol into solution. Cholesterol was then determined as outlined by Zlatkis[20].*

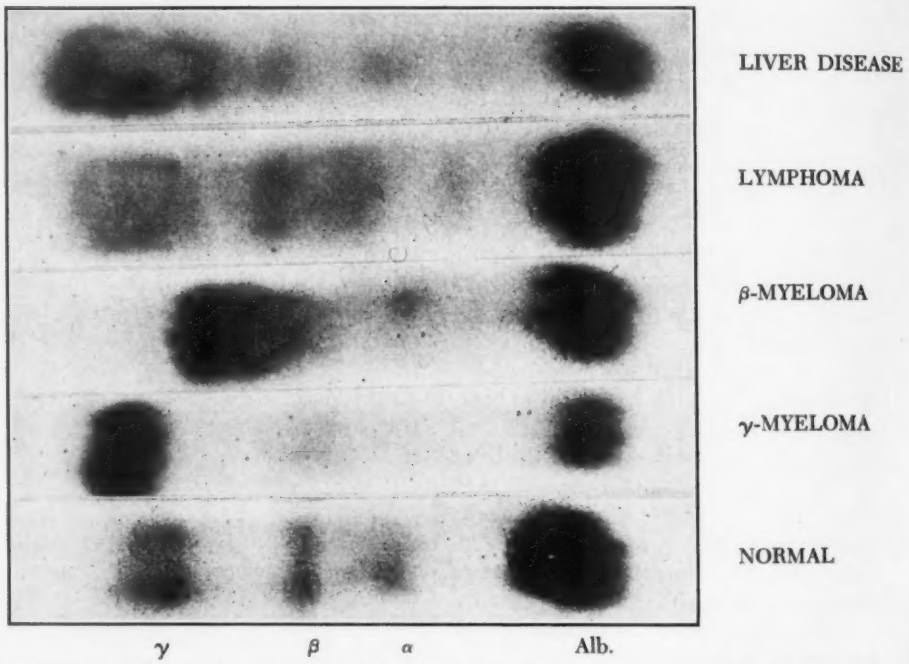

Fig. 1.—Paper electrophoretic distribution of serum proteins in normals and in patients with various diseases (see text).

*The γ-globulin electrophoretic fraction includes nonmigrating lipids and cholesterol, with this technique.

Results. Our results are summarized in Tables 1, 2, 3, 4 and 5 and Figs. 1, 2, 3 and 4.

a) "HEALTHY" SUBJECTS (Table 1). Electrophoretic distribution of various protein fractions was similar to that described by other authors (Fig. 1). It should be mentioned that, as pointed out by Durrum[5], the concentration of serum albumin determined by direct spectrophotometric readings of bromphenol blue scanning patterns on dry paper strips at 595 λ was relatively low as compared to results of other techniques.

In fasting subjects, cholesterol appeared bound in various proportions to all protein fractions (Table 1, Fig. 4), with preference for β-globulin. Albumin-bound cholesterol was relatively constant (20.34 ± 1.37%), while wider variations were found in cholesterol bound to the α-globulin (15.79 ± 3.2%), β-globulin (38.02 ± 2.5%) and γ-globulin (34.93 ± 4.2%) fractions. Administration of a fatty meal (2 eggs, 20 gm. of animal butter and 200 ml. of milk) was followed by rise in total serum cholesterol level, also by moderate change in the percentage distribution of the cholesterol bound to the various protein fractions. Most commonly, these variations consisted of increase of β-globulin-bound and diminution of γ-globulin-bound cholesterol.

Of the lipids, approximately 70% were found to be bound to β- and γ-globulin fractions; the rest bound to albumin and α-globulin fractions (Fig. 2). No significant change of this distribution pattern was seen following the administration of a fatty meal.

Carbohydrates distributed themselves among proteins fractions, α-globulin fraction containing their greatest amount (Fig. 3). After a fatty meal, however, β-globulin fraction was found to contain an increased amount of glycoproteins.

TABLE 1.—ELECTROPHORETIC MIGRATION OF PROTEIN-BOUND CHOLESTEROL AND LIPOPROTEINS IN NORMAL SUBJECTS, BEFORE AND AFTER FATTY MEAL*

					Albumin			*α-Globulins*			*β-Globulins*			*γ-Globulins*		
Initials	*Age*	*Sex*		*Total Protein gm. %*	*Cholesterol mg./100 ml.*	%	*Bound Cholesterol %*	*Bound Lipids %*	%	*Bound Cholesterol %*	*Bound Lipids %*	%	*Bound Cholesterol %*	*Bound Lipids %*	%	*Bound Cholesterol %*	*Bound Lipids %*
S.M.	27	M	Fasting	7.2	140	60	20.45	22	6	10.44	12	12	29.59	25	24	39.46	41
			A. meal	7.6	260	58	16.10	20	5	5.19	12	15	49.10	35	24	29.61	33
H.M.	31	M	Fasting	6.9	240	58	18.35	22	8	20.05	10	12	29.33	27	22	28.27	41
			A. meal	7.2	279	58	20.83	23	8	23.82	14	12	16.14	18	22	39.21	43
M.S.	38	M	Fasting	7.9	216	59	16.00	18	6	20.9	15	10	16.90	17	25	46.20	50
			A. meal	7.9	270	56	15.84	17	4	18.33	14	15	30.00	27	25	35.83	42
L.M.	21	F	Fasting	8.0	250	60	22.10	20	6	4.6	8	12	32.10	27	22	41.20	45
			A. meal	8.2	300	60	28.75	22	8	22.87	14	14	22.30	21	18	25.85	43
M.St.	18	F	Fasting	7.3	250	55	24.80	20	9	23.50	15	15	32.20	25	22	19.50	40
			A. meal	7.6	320	57	23.85	18	8	21.33	14	17	39.00	29	18	15.82	39

* Each column gives the percentage concentration of the protein fraction concerned and the percentage of total cholesterol and lipids bound to that particular fraction.

TABLE 2.—CHOLESTEROL AND CHOLESTEROL ESTERS IN VARIOUS TYPES OF LYMPHOMA*

					Relapse		*Remission*	
No.	*Initials*	*Age*	*Sex*	*Diagnosis*	*Cholesterol mg./100 ml.*	*Esters Per Cent*	*Cholesterol mg./100 ml.*	*Esters Per Cent*
1.	A.S.	27	M	Hodgkin's granuloma	108	52	145	76
2.	V.W.	34	M	Hodgkin's granuloma	105	60	193	78
3.	T.W.	59	M	Hodgkin's granuloma	101	49	162	72
4.	V.T	21	M	Hodgkin's granuloma	79	32	147	68
5.	H.H.	27	F	Hodgkin's granuloma	142	65	176	75
6.	C.S.	35	F	Hodgkin's sarcoma	98	47	184	70
7.	D.G.	47	F	Hodgkin's sarcoma	107	38	135	67
8.	C.O'D.	52	M	Hodgkin's sarcoma	116	49	149	66
9.	P.MacH.	30	M	Hodgkin's sarcoma	92	51	175	78
10.	B.Z.	17	F	Hodgkin's sarcoma	87	37	98	52
11.	D.Z.	62	M	Lymphosarcoma	123	38	140	49
12.	N.S.	18	F	Lymphosarcoma	109	29	170	53
13.	F.O'C.	26	M	Lymphosarcoma	101	55	158	78
14.	G.D.	35	M	Lymphosarcoma	34	42	102	74
15.	E.G.	61	M	Lymphosarcoma	67	44	117	74
16.	D.C.	71	M	Lymphosarcoma	115	71	175	78
17.	E.M.	27	F	Lymphosarcoma	122	46	190	66
18.	G.R.	38	M	Lymphosarcoma	85	57	211	68
19.	M.R.	46	F	Lymphosarcoma	94	49	143	78
				Average values.....	99.2	49	156.3	68.9

* Method of Schönheimer and Sperry—Normal Values: Cholesterol 150 to 250 mg./100 ml., esters 70 to 80 per cent.

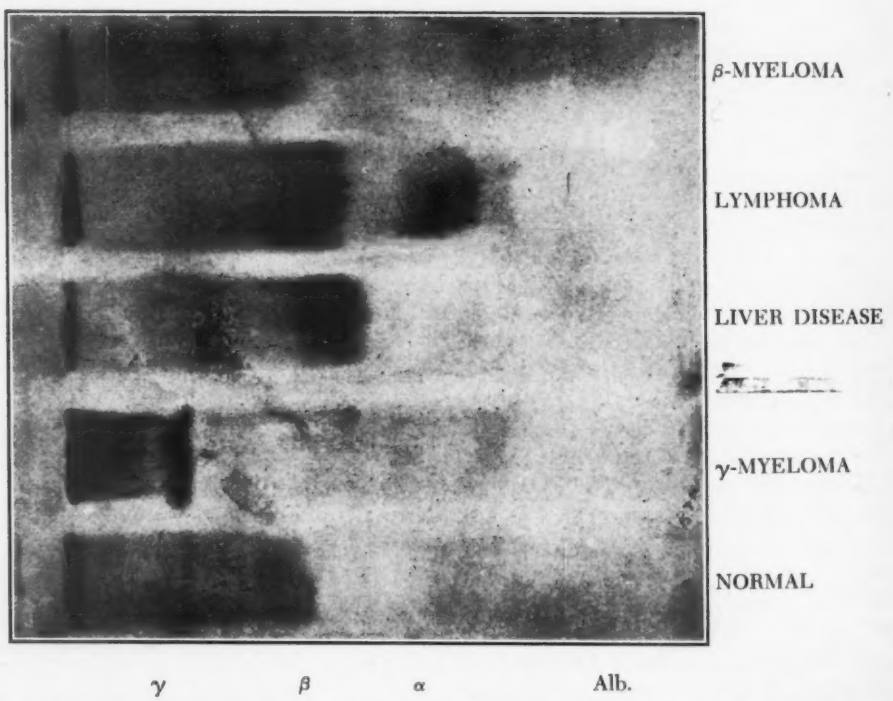

Fig. 2.—Paper electrophoretic migration of serum lipoproteins in normals and in patients with various diseases (see text).

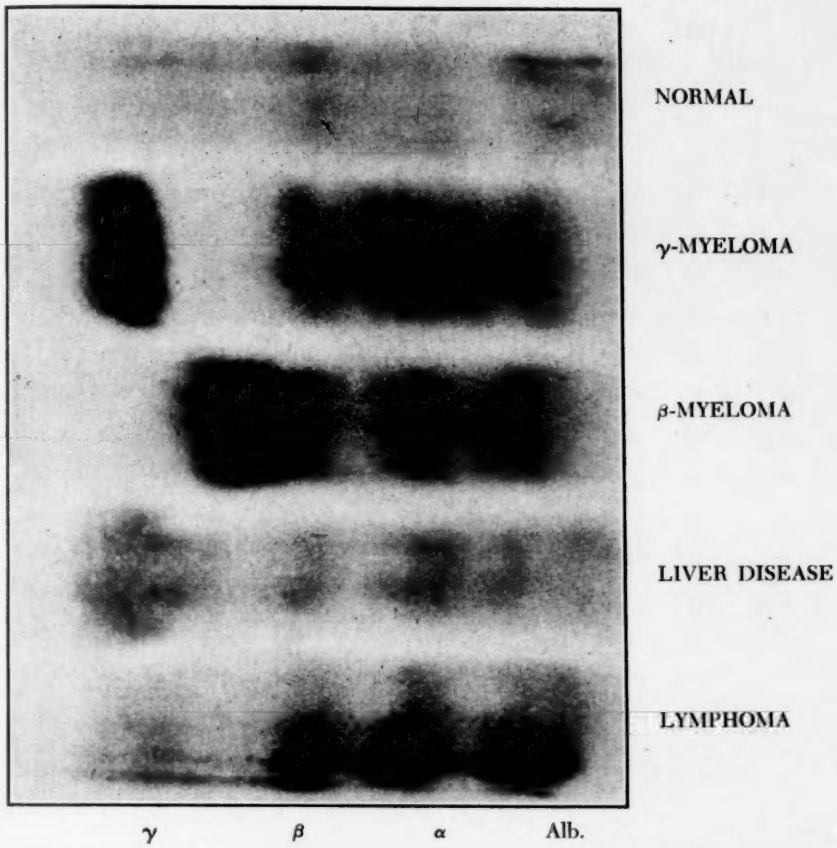

Fig. 3.—Paper electrophoretic migration of serum glycoproteins in normals and in patients with various diseases (see text).

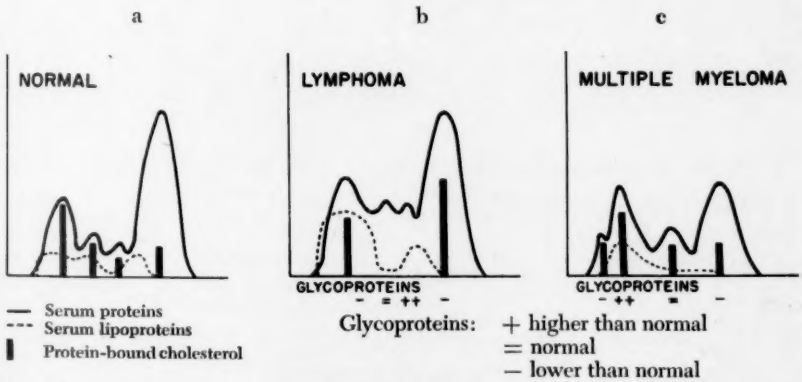

Fig. 4.—Graphic relationship of serum proteins, lipoproteins, glycoproteins and proteins and protein-bound cholesterol in (a) normal subject; (b) patient with lymphoma; (c) patient with multiple myeloma.

TABLE 3.—ELECTROPHORETIC MIGRATION OF PROTEIN-BOUND CHOLESTEROL

Initials	*Age*	*Sex*	*Diagnosis* (*relapse or remission*)	*Total Protein* gm. %	*Cholesterol* mg./100 ml.	*Albumin* %	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
H.W.	29	M	Hodgkin's granuloma (relapse)	7.1	172	31	31	20	++
H.R.	36	M	Hodgkin's granuloma (relapse)	6	130	34	30.1	5	+
W.W.	81	M	Hodgkin's granuloma (relapse)	5.9	200	36	29.2	20	+
L.A.	27	M	Hodgkin's sarcoma (relapse)	3.5	138	25	30.1	0	+
F.D.	9	M	Hodgkin's granuloma (after cortisone)	6.8	210	32	16.3	12	—
M.A.	33	F	Hodgkin's sarcoma (remission)	7.2	230	45.6	13.5	0	+
M.G.	38	M	Hodgkin's sarcoma (remission)	6.9	180	48	18.2	0	—
B.L.	62	M	Lymphosarcoma (relapse)	6.2	170	32	57.10	17	—
M.I.	34	F	Lymphosarcoma (relapse)	5.8	150	34.5	59.26	20	++
W.B.	42	M	Lymphosarcoma (relapse)	5.7	170	35.5	32.4	0	=
M.D.	81	F	Lymphoblastoma (remission)	7.3	230	42	30.6	18	+
E.C.	43	M	Giant follicular lymphoblastoma (relapse)	3.5	102	28	35	12.5	++

(*) Bound carbohydrates
(+) : Increased amount

TABLE 4.—ELECTROPHORETIC MIGRATION OF PROTEIN-BOUND CHOLESTEROL

Initials	*Age*	*Sex*	*Total Protein* gm. %	*Cholesterol* mg./100 ml.	*Albumin* %	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
G.A.	60	F	12.7	210	29	26.3	5	=
McS.R.	57	F	8.6	170	28	20	0	—
D.S.	55	M	10.2	190	35	15.85	4	—
N.B.	62	F	8.3	168	33	19.25	4	—

(*) : Bound carbohydrates
(+) : Increased amount

TABLE 5.—ELECTROPHORETIC MIGRATION OF PROTEIN-BOUND CHOLESTEROL

Initials	*Age*	*Sex*	*Total Protein* gm. %	*Cholesterol* mg./100 ml.	*Albumin* %	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
H.B.	52	F	8.4	145	34	14.55	17.2	—
R.P.	42	M	6.2	150	48.6	11.35	0	—

(*) : Bound carbohydrates
(+) : Increased amount

LIPIDS AND CARBOHYDRATES IN PATIENTS WITH VARIOUS TYPES OF LYMPHOMA

α-Globulins				*β-Globulins*				*γ-Globulins*			
%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
23.5	24	20	+	20.5	10	12	+	25	35	48	=
16	22.9	35	+	23	15	9	—	27	32	51	—
17	18.3	23	++	23	12.5	34	=	24	40	14	—
35	26.6	0	+	15	16	33.5	—	25	27.3	66.5	—
20	31	14	+	14	25	34	—	24	27.7	40	—
18	22.9	23	+	16.4	29.7	26	—	20	33.9	51	—
10	24	38	+	20	16	8	—	22	41.8	54	—
33	0	0	—	13	0	35	±	22	42.9	48	—
20.5	0	24	++	13.5	0	8	=	31.5	40.74	48	—
17	13.5	21.4	+	26.4	32.4	7.1	—	21.1	21.7	71.5	—
16	6.4	25	+	20	19.8	33.5	=	22	43.2	33.5	—
22	28.75	12.5	+	25	12.5	25	=	25	23.75	50	—

(=) : Normal amount
(—) : Decreased amount

LIPIDS AND CARBOHYDRATES IN PATIENTS WITH MULTIPLE MYELOMA

α-Globulins				*β-Globulins*				*γ-Globulins*			
%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
18	18.2	0	=	24.9	29.20	10	—	28.1	26.3	85	+
21	20.7	0	=	16	30	10	—	35	29.3	90	+
6	18.3	5	=	14	28.45	12	—	35	37.4	79	+
14	20.35	5	=	41	40.4	83	++	12	20	8	—

(=) : Normal amount
(—) : Decreased amount

LIPIDS AND CARBOHYDRATES IN PATIENTS WITH PARENCHYMAL LIVER DISEASE

α Globulins				*β-Globulins*				*γ-Globulins*			
%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)	%	*Bound Cholesterol* %	*Bound Lipids* %	*Bound Carbohydrates* (*)
4.7	13.20	8.6	—	32	40.9	26.2	=	29.3	31.35	48	+
9.2	10.7	7	—	19.4	39.25	23	=	23.8	38.70	70	+

(=) : Normal amount
(—) : Decreased amount

b) LYMPHOMA (Table 3 and Figs. 2, 3, 4). This study included 31 cases of lymphoma of various types. In 19 serum cholesterol and esters only were studied both in stage of remission and in relapse; in 12, complete electrophoretic studies were carried out.

In all cases with active disease the serum cholesterol level and percentage of cholesterol esters were decreased. Remission was followed by elevation of total as well as of esterified cholesterol (Table 2). Also in all cases with active disease the serum total protein was decreased. Albumin/globulin ratio was usually inverted (Fig. 1). The α-globulin fraction was increased in all cases; β- and γ-globulin fractions were increased only occasionally. Thus there was marked hypo-cholesterinemia as well as severe abnormality of serum protein fraction distribution in all instances of active lymphoma.

Protein-bound cholesterol was increased constantly in the albumin and less constantly in the α-globulin fraction, decreased in the β-globulin fraction in all cases in relapse. Lipoproteins followed a normal pattern in 7 cases; were slightly increased in albumin and α-globulin fractions in 5 (Fig. 2). Glycoproteins were slightly decreased in the albumin, β- and γ-globulin fractions, and markedly increased in the α-globulin fraction in most cases (Fig. 3).*

c) MULTIPLE MYELOMA (Table 4). Total proteins were increased in all cases, γ-globulin being the predominant fraction in 3 cases and β-globulin in one (Fig. 1). Total serum cholesterol, and distribution of cholesterol in the various protein fractions were normal. As previously described by other authors[4,8,12,13,17,18] there was considerable increase in the amount of lipids and carbohydrates bound to the pathologically elevated serum protein fractions (Figs. 2, 3 and 4).

Discussion. As mentioned in the introduction, studies of electrophoretic migration of protein-bound blood constituents in hematologic disorders have been few thus far. Striking abnormalities in serum protein pattern have been found in patients with multiple myeloma[12,17]. Our results show that they are of lesser magnitude but of equal significance of lymphoma. In addition, changes in cholesterol and cholesterol esters were found in the lymphoma group. These were striking enough to be of possible diagnostic value.

CHOLESTEROL AND PROTEIN-BOUND CHOLESTEROL IN LYMPHOMA. There was apparently direct relationship between activity of the disease, serum protein distribution and serum cholesterol level. Values of serum albumin, total cholesterol and cholesterol esters were low in general relation to the severity and extension of the active disease; as remission set in, these values reverted toward normal. Serum globulin fractions exhibited an opposite trend. This pattern was fairly characteristic of the disease. Behavior of protein-bound cholesterol was probably of equal significance. In patients with active lymphoma cholesterol was preferentially

*One of the patients in this group (E.C.) developed obstructive jaundice due to pressure of enlarged lymph nodes on the biliary tract. As a result of this complication, there were a few appreciable changes in serum protein pattern, with relative increase of albumin and decrease of β-globulin fraction as compared to previous findings. Distribution of lipo- and glycoproteins were essentially unmodified. Cholesterol level rose to 650 mg. per 100 ml., but esters dropped to a very low value (15%). The greatest percentage of cholesterol appeared bound to γ- and β-globulin (53.0 and 21.0% respectively), a behavior similar to that found in liver disease. The most interesting finding was perhaps, the permanence of serum cholesterol esters at a low level, indicating a basic abnormality of the metabolism of this substance, even when its absolute concentration in the serum was much elevated.

bound to the serum albumin fraction although this was decreased, and to α-globulin. In state of remission, cholesterol was preferentially bound to β-globulin, as in normal individuals. Nothing more than a working hypothesis can be offered to explain these findings. It is likely that abnormalities of serum cholesterol and esters and of distribution of serum proteins reflect anomalies of synthesis of proteins and cholesterol and of esterification of cholesterol. Mechanism of these anomalies is entirely obscure. Equally difficult to interpret are the described changes in electrophoretic mobility of protein-bound cholesterol. These are apparently independent of abnormal distribution of serum protein fractions alone. Thus, in parenchymal liver disease we also found decrease in serum albumin and increase in globulin fractions, but cholesterol, as in normal subjects, was preferentially bound to β-globulin and lipo- and glyco-proteins were predominantly found in β and γ fractions (Table 5).

The behavior of protein-bound cholesterol thus seemed typical of lymphoma; perhaps, of some diagnostic value.

LIPOPROTEINS AND GLYCOPROTEINS IN LYMPHOMA. Lipoprotein changes were similar to those described for protein-bound cholesterol, but they were considerably less constant. Evaluation of changes in electrophoretic mobility of glycoproteins in lymphoma was made difficult by poor knowledge of their behavior in normal conditions. In general, we found decrease of albumin-bound and γ-globulin bound and increase of α-globulin bound carbohydrates. While the latter finding was common to patients with high fever or suffering from malignancies[6,7], the former finding has, thus far, been seen only in lymphoma.

BOUND CHOLESTEROL, LIPO- AND GLYCOPROTEINS IN MULTIPLE MYELOMA. Our results do not help to dissipate the confusion existing in the literature. Serum cholesterol level has been found to be normal[17], high[9,17,18] or low[12] by different authors. It was normal in our 4 cases, irrespective of the predominant serum protein fraction. Protein-bound cholesterol has been found tied primarily to the increased globulin fractions[13]; we disagree with these findings, since we find almost normal cholesterol distribution in our 4 cases. Regarding lipoproteins, Lewis and Page[12] found no correlation between changes in serum protein pattern and lipoprotein distribution using ultracentrifugation techniques. However, Nikkilä[13] by paper electrophoresis techniques found an increase of lipoproteins in the α_2 and β fractions, irrespective of the type of myeloma. Sachs[17] found that lipids were concentrated in the fraction which was pathologically increased. Our findings agree closely with those of Sachs *et al.* There is no question that the diversity of technical tools, considerable difficulty in correct determination of protein electrophoretic mobility in multiple myeloma and the very abundance of the proteins with likely phenomena of absorption may account for the disparity of the results. Our findings with respect to glycoproteins agree closely with those of Sachs *et al.*[17] who showed that carbohydrates are found in higher concentration in the pathologically increased protein fraction.

Summary. 1. A simple technique has made possible the study of electrophoretic mobility of protein-bound cholesterol in normal individuals and patients with lymphoma and multiple myeloma. These studies have been extended to the analysis of the electrophoretic behavior of the lipo- and glycoproteins in these diseases. 2. In lymphoma, total cholesterol and cholesterol esters are

strikingly and characteristically decreased in relapse and tend to revert to normal in remission. Protein-bound cholesterol is increased in the albumin and α-globulin fractions and decreased in β-globulin fractions in patients with active disease. Lipoproteins and glycoproteins follow a similar but less striking and predictable pattern. Alterations of free, esterified and protein-bound cholesterol are fairly typical of lymphoma and found almost exclusively in advanced stages of the disease. They are not due simply to abnormalities in the distribution of serum proteins since they are not found in parenchymal liver disease, where serum protein changes are similar to those seen in lymphoma. 3. In multiple myeloma, serum cholesterol level is normal and normally distributed among protein fractions; lipoproteins and glycoproteins are preferentially associated with the pathologically increased protein fractions. Similar alterations occur in liver disease.

ADDENDUM: After the submission of this manuscript, an essentially similar method for determination of protein-bound cholesterol has been published by Jencks and Durrum (J. Clin. Invest., **34**, 1437, 1955).

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(Interlingua on page 191)

THE DEGREE OF CORONARY AND AORTIC ATHEROSCLEROSIS IN NECROPSIED CASES OF MULTIPLE MYELOMA

By David M. Spain, M.D.

Irving J. Greenblatt, Ph.D.

Isidore Snapper, M.D.

and

Theodore Cohn, M.D.

(From the Department of Laboratories and the Messinger Research Laboratories of Beth-El Hospital, Brooklyn, New York)

In studies on the pathogenesis of human atherosclerosis particular attention has been accorded to the hypercholesterolemic states that are often present in the nephroses, diabetes mellitus, hypothyroidism, xanthomatoses and familial hyperlipemia. In these conditions generally greater degrees of atherosclerosis have been found for the comparable age and sex than in the "normal" population. However, there has been little or no opportunity to study the extent of atherosclerosis in non-rectified hypocholesterolemic states. Such studies as those by Wilens[2] on the state of nutrition as related to the degree of atherosclerosis, encompassed a wide variety of situations not necessarily associated with low serum cholesterol levels. Recently, Greenblatt *et al.*[1] have demonstrated that in multiple myeloma the serum beta lipoprotein levels in the Sf_{12-20} and Sf_{20-100} classes are often low. These classes of serum beta lipoproteins are the ones reported to be most often related to the development of atherosclerosis. They have also demonstrated that patients with multiple myeloma not infrequently have rapid plasma lipid clearances following test meals of olive oil. Based upon these facts and the experience of one of the authors (I.S.) that he could not find in his records a case of coronary occlusion in an extensive series of patients with multiple myeloma, it was decided to analyze the degree of coronary and aortic sclerosis on necropsied cases of multiple myeloma.

As mentioned previously Wilens reported a striking relationship between the state of nutrition during health and during final illness and weight loss with the amount of coronary and aortic atherosclerosis observed upon postmortem examination. He accounted for this on the basis of the resorption of arterial atheromatous deposits during the period of wasting disease. For this reason a control group of consecutively necropsied cases who had died from cancer (mainly of the colon and stomach), and who had evidence of malnutrition, was similarly studied. These cancer cases were not known especially to have low serum cholesterol levels or rapid plasma lipid clearances. Another group of necropsied individuals who had died suddenly as a result of accident, homicide or suicide were selected to serve as "normals." Each group consisted of 104 cases of which the sex and the age distribution may be noted in Table 1.

The degree of atherosclerosis as observed in the coronary arteries and

aorta was classified as either minimal, moderate or advanced, based upon the recorded observations in the necropsy protocol. The number of consecutive cancer cases studied was similar to the number of multiple myeloma cases studied in each institution. The "normals" were cases selected from the Medical Examiner's Office of Westchester County.

Results. The findings in the three groups studied can be noted in Table 1. In the multiple myeloma group, 82 cases revealed minimal sclerosis whereas in the cancer group half of this number were minimal and in the "normals" only one-fourth. The reverse was observed in regard to the advanced degrees of atherosclerosis. Thus, the amount of atherosclerosis was significantly less in the multiple myeloma group than in the cancer group despite similarities in age, sex and terminal state of nutrition. The difference between the multiple myeloma group and the "normals" was even more striking in view of the fact that the "normals" were of somewhat younger age.

TABLE 1.—THE DEGREE OF CORONARY AND AORTIC ATHEROSCLEROSIS IN NECROPSIED CASES OF MULTIPLE MYELOMA, CANCER AND "NORMALS"

Type of Case	*Number of Cases*	*Mean Age S.D.*	*Degree of Atherosclerosis*		
			Minimal	*Moderate*	*Advanced*
Multiple myeloma	104 (69 male) (35 female)	56 ± 2.0	82	14	8
Cancer	104 (65 male) (39 female)	60 ± 2.2	43	39	22
"Normals"	104 (74 male) (30 female)	53 ± 2.8	18	54	32

Discussion. The minimal degree of atherosclerosis noted in the multiple myeloma cases cannot be accounted for simply on the basis of the terminal wasting process since the degree of sclerosis was much lower in this group than the cancer cases who usually had more marked degrees of malnutrition. This lesser amount of atherosclerosis probably results from the failure to deposit new lesions and to the resorption of those lesions still in a reversible state during the period of illness. In 17 cases serum cholesterol determinations had been performed. In 15 of these, the serum cholesterol levels were below 200 mg. per 100 ml. with such representative values as 36, 93, 100, 120, 121, 126 mg. per 100 ml. Thus the observations that patients with multiple myeloma often exhibit extremely rapid plasma clearances and also reveal low serum cholesterol levels may be important factors in the small amount of atherosclerosis present in these patients. Perhaps related to these disturbances of lipid transport is the alteration in the synthesis of proteins that has been reported in patients with multiple myeloma.

Analysis of the 8 cases of myeloma that showed advanced sclerosis revealed 2 in whom serum cholesterol determinations had been performed. These were 314 and 300 mg. per 100 ml. and were in contrast to the low levels encountered in other cases. One of the other cases with advanced sclerosis had had severe diabetes mellitus for many years, and another had had hypertension for many years. Of interest was the finding of only scant atherosclerosis in a 63-year-old male with severe hypertension for many years whose heart on postmortem examination weighed 820 gm.

The findings of lesser degrees of

sclerosis than would originally be expected for the age and sex of the cases involved would appear to add further significance to the role of cholesterol metabolism and lipid transport in the pathogenesis of human atherosclerosis.

Conclusion. 1. Studies on a necropsied series of 104 cases of multiple myeloma revealed significantly less atherosclerosis in the aorta and coronary arteries than in corresponding groups of cancer cases and "normals."

2. This lesser degree of atherosclerosis in myeloma cases is often associated with low serum cholesterol levels and rapid plasma lipid clearances.

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SUMMARIO IN INTERLINGUA

Le Grado de Atherosclerosis Coronari e Aortic in Casos Necropsiate de Myeloma Multiple

1. Studios necroptic de un serie de 104 casos de myeloma multiple revelava, in comparation con correspondente series de patientes de cancere e de subjectos normal, significativemente minus atherosclerosis del aorta e del arterias coronari.

2. Iste grado inferior de atherosclerosis in casos de myeloma es frequentemente associate con basse nivellos seral de cholesterol e un rapide clearance de lipido plasmatic.

MYOCARDITIS IN VIRAL (EPIDEMIC) HEPATITIS*

By Otto Saphir, M.D.

George D. Amromin, M.D.

and

H. Yokoo, M.D.

(From the Department of Pathology,** Michael Reese Hospital, Chicago, Illinois)

It is well known that myocarditis may constitute a serious complication of virus diseases. Poliomyelitis, measles, mumps, viral pneumonias, encephalitis, and infectious mononucleosis, although its viral cause was never proved, are some in which myocarditis has been described. There are only a few reports of its occurrence in viral hepatitis. Because of the apparent importance of myocarditis as a serious complication and the increasing incidence of hepatitis, we thought it of interest to study pertinent cases.

Myocardial changes in viral hepatitis have been rarely reported in the literature. Lyon[4] mentioned the occurrence of myocarditis in epidemic hepatitis. Adler and Lyon[1] reported on cardiac disorders associated with infectious hepatitis. However, they referred only to electrocardiographic changes. Dehn *et al.*[2] also described electrocardiographic changes in cases of infectious hepatitis. Lucké[6] mentioned only hemorrhages in the heart, located in the epicardium and commonly beneath the septal endocardium of the left ventricle near the undefended space. While Lucké and Mallory[7] referred to the various changes in a number of organs in observations on the fulminant form of epidemic hepatitis, they did not mention myocardial changes. Wood[11] found in one of his 10 cases definite myocarditis characterized by infiltration of lymphocytes and mononuclear phagocytes. These were more numerous beneath the endocardium and in the papillary muscles. Lyon[5] (1952) noted parenchymatous degeneration of the cardiac muscles, to which the term myocardosis was applied. He also mentioned frequent electrocardiographic changes in various types of primary liver diseases. Eisen and Markovich[3] noted severe hemorrhagic manifestation with a hemorrhagic pericardial exudate. Microscopically, sections of the pericardial surfaces disclosed foci of hemorrhage and intense, nonspecific inflammatory reaction of lymphocytes, neutrophils, plasma cells, mononuclear elements and scattered fibroblasts. These changes were sharply demarcated from the unchanged myocardium.

This study is based on a re-examination of the clinical records and necropsy findings of four instances of viral (epidemic) hepatitis. Although their viral nature cannot be proven, it seems quite clear that the histopathologic changes in the liver in these cases correspond well to the concept of viral hepatitis. Only a very short outline of the pertinent histories and findings will be given.

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Case Reports. CASE 1. The first patient* was a 54-year-old white female who had an upper gastrointestinal upset 2 weeks before admission after which jaundice appeared. There was no history of previous blood or plasma transfusions. On examination, she was deeply jaundiced. The heart was slightly enlarged to the left and there was a systolic murmur in the region of the third and fourth left interspaces. Bilirubin but no urobilinogen was found in the urine. The serum alkaline phosphatase was 16.5 units, the total serum protein 9 gm. per 100 ml. with 6 gm. globulin. The serum bilirubin was 39.6 mg. per 100 ml., the cholesterol 140 mg. per 100 ml. with 27.5% esters. Cephalin flocculation was 4 plus. The patient rapidly went into coma and the jaundice deepened. The blood pressure was 100/60, temperature 98.6°, pulse rate 80. She died on the second hospital day.

At necropsy the patient was severly jaundiced. There were 250 ml. of clear fluid in the peritoneal cavity. Only the most important findings will be given. The heart weighed 340 gm. and the epicardium was normal. There was an old endocarditis of the aortic and mitral valves, seemingly of the rheumatic type. Just beneath the endocardium of the left ventricle in the region of the interventricular septum there was an area of subendocardial hemorrhage measuring about 1 × 1.5 cm. in greatest dimension. The liver was markedly shrunken, soft, and weighed 810 gm. Its capsule was wrinkled and the color varied from red-purple to red-brown. Over the surface were yellowish-green, slightly raised nodules measuring from 1 to 3 mm. in thickness. The kidneys weighed 310 gm., were soft and deep brown-green.

Microscopically, the myocardium disclosed a moderate amount of newly formed, focally hyalinized connective tissue, most marked in the region just beneath the aortic cusps. The base of the latter also showed much fibrosis and hyalinization with a number of newly formed blood vessels and occasional accumulations of lymphocytes at the base of the valve. These changes appeared to be quite consistent with an old endocarditis of the rheumatic type. Throughout the myocardium there was also a moderate perivascular fibrosis with an occasional lymphocyte or endothelial leukocyte. In other areas there was a varying amount of fibrous tissue interrupting the course of the muscle fibers. In a number of sections, however, an entirely different histologic picture presented itself. There were areas where the muscle fibers were spread by an edema-like material which contained a few lymphocytes, myocardial reticulocytes and polymorphonuclear leukocytes. An occasional muscle fiber appeared necrotic. (See Figs. 1 and 2.)

The most outstanding changes, however, were found in the interventricular septum, close to the areas of the subendocardial hemorrhages which were more or less confined to the region of the left bundle of His. In a number of sections, where the branches of the bundle could easily be identified, they were flanked on two sides by many extravasated red blood corpuscles. The muscle fibers of the bundles showed varying degrees of cloudy swelling and also outspoken foci of necrosis. However, in other sections where there were no hemorrhages, the muscle bundles were surrounded by polymorphonuclear leukocytes. These cells also extended into the adjacent regions of the myocardium itself. Foci of muscle necrosis were found not only in the bundle but also in the adjacent myocardium. The blood vessels showed no changes of note.

To summarize: A patient with an old history of endocarditis developed viral hepatitis and died rather rapidly. Acute myocarditis was found in addition to older inflammatory changes in the myocardium and aortic valve. The acute myocarditis was diffuse and also affected in a more localized fashion the region of the left bundle of His where there were also foci of hemorrhages. Characteristic were small areas of muscle fiber necrosis.

CASE 2. The second patient† was a 33-year-old white female who was admitted because of acute cramping pains in the right upper quadrant associated with jaundice. There was a history of receiving a "flu shot" 4 months prior to admission. On physical examination she was not in acute distress. There was a deep right upper quadrant tenderness. During her hospital stay the jaundice increased in severity. Coincidently she became mentally confused. A few ecchymoses developed over the body and sclerae. The area

*We are indebted to Dr. H. Krasso for the use of the clinical record.

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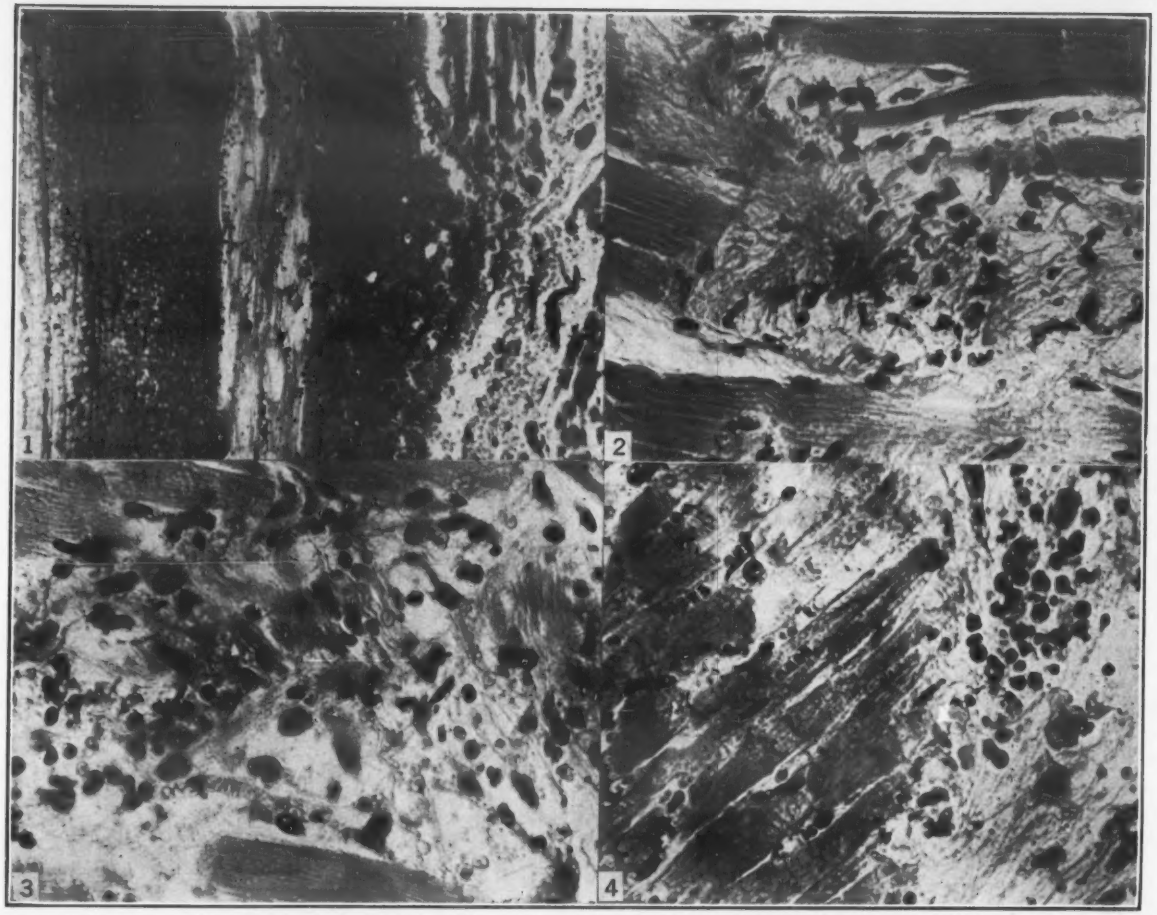

Fig. 1.—Section of the myocardium through the left bundle of His. Note the hemorrhage and the encroachment upon the muscle bundles. × 300. Hematoxylin and eosin preparation.

Fig. 2.—Note inflammatory cells and the degenerative changes and necrosis of muscle fibers. × 450. Hematoxylin and eosin preparation.

Fig. 3.—Foci of necrotic muscle fibers with few lymphocytes and polymorphonuclear leukocytes. × 450. Hematoxylin and eosin preparation.

Fig. 4.—Note the destruction of muscle fibers and the presence of a few polymorphonuclear leukocytes, lymphocytes, and myocardial reticulocytes. × 450. Hematoxylin and eosin preparation.

of the liver dullness decreased and the liver edge could not be palpated. She gradually become comatose and expired in coma. The urine showed no urobilinogen but bilirubin was present. The serum bilirubin was 39.6 mg., serum cholesterol 156 mg., cholesterol esters 32.2%. Thymol turbidity test was 2.1 and 4.2 units and the cephalin-cholesterol flocculation was 4 plus. The alkaline phosphatase was 9.8 units, and the prothrombin time 50% of normal. The temperature was 103° with a pulse rate of 96 to 112. She died 21 days after admission. The electrocardiogram* showed the following: rate 81, P–R interval 0.18 sec., low voltage in all limb and chest leads, S–T depressed in lead 2, T small and inverted in V–2, S–T depressed in V–5 and 6, S–T elevated in $_{a}V_{R}$; intermediate position; transition zone in normal position; sinus rhythm; nonspecific abnormalities.

At necropsy the skin was markedly jaundiced and of a deep green to orange-tinged yellow. The abdominal cavity contained 4,000 ml. of a clear yellow liquid. The heart weighed 240 gm. There were a number of subepicardial petechial hemorrhages and a few small and larger subendocardial hemorrhages within the left ventricle. The liver was generally yellow-tan and shrunken, weighing 800 gm. The liver lobes were disproportionately smaller and the capsule was finely wrinkled. On section there was a complete distortion of the normal architecture with large red hemorrhagic areas adjacent to elevated yellow-green nodular patches and flat tan fleshy areas. The kidneys were markedly enlarged, weighing 510 gm. They were dark green and contained a number of petechial hemorrhages throughout the surface. Also, the pelves and ureters showed submucosal hemorrhages.

Microscopic sections of the myocardium disclosed many areas of interstitial edema with a few interspersed lymphocytes and polymorphonuclear leukocytes. Outstanding, however, were small foci of necrosis of muscle fibers which were either surrounded or partially replaced by myocardial reticulocytes, a few lymphocytes and polymorphonuclear leukocytes. Often the former two cell types predominated and there were only a few granulocytes. The adjacent endocardium also showed a few inflammatory cells. Occasionally also adjacent interstitial spaces were infiltrated by these cells. Often only minute foci of necrosis in muscle fibers were seen. In other fields typical localized abscesses were seen. In their midst rare clumps of cocci resembling staphylococci could be noted. Minute foci of necrosis with a few inflammatory cells were also present just beneath the endocardium, in the region of the bundle of His. The latter consisted of lymphocytes with a few polymorphonuclear leukocytes intermingled with red blood corpuscles. Abscesses were also seen in both kidneys.

In summary: A 33-year-old female who developed an increasingly severe jaundice showed in addition to hepatitis, myocarditis which was both diffuse and focal. The latter was characterized by necrosis of muscle with many inflammatory cells which were also found just beneath the endocardium. In addition there were also typical abscesses in the myocardium and kidneys.

CASE 3. The third patient** was a 49-year-old Negro male who was admitted as an emergency with slight jaundice, chills and fever, and emesis followed by pain. The patient was in shock with a blood pressure of 50/20, pulse 140, and temperature of 101° F. He vomited 400 ml. of green, bile-colored material. Levophed was started to combat shock with only slight response. The patient became comatose and the temperature climbed to 106.2° F. He died 2 days after admission to the hospital. Serial electrocardiograms taken shortly before death disclosed the following:

The first electrocardiogram was reported as showing a rate of 136; P–R interval 0.14 sec.; P, QRS and T small in 1; P large and pointed in 2, 3, and $_{a}V_{F}$; S–T slightly depressed in 3 and $_{a}V_{F}$, slightly elevated in $_{a}V_{R}$ and $_{a}V_{L}$; T notched in V–2 and in V–3; sinus tachycardia; semivertical position; P–pulmonale; a definitely abnormal curve: such records are seen in chronic pulmonary diseases (pulmonary emphysema).

The second electrocardiogram was reported as showing a rate of 167 (notably faster than before); P–R interval 0.14 sec.; QRS more upright in 1, mainly inverted in 2 and 3; T indiscernible in 1,

Fig. 2.—Note inflammatory cells and the degenerative changes and necrosis of muscle fibers. × 450. Hematoxylin and eosin preparation.
Fig. 3.—Foci of necrotic muscle fibers with few lymphocytes and polymorphonuclear leukocytes. × 450. Hematoxylin and eosin preparation.
Fig. 4.—Note the destruction of muscle fibers and the presence of a few polymorphonuclear leukocytes, lymphocytes, and myocardial reticulocytes. × 450. Hematoxylin and eosin preparation.

*We are grateful to Dr .R. Langendorf for reviewing the electrocardiograms.

**We are indebted to Dr. N. Sloane for the use of the clinical record.

smaller in 2 and 3; QRS upright in $_aV_L$, mainly inverted in $_aV_F$; T less inverted in $_aV_L$; T less upright in V–4 to V–6; sinus tachycardia; semihorizontal position; P–pulmonale; definitely abnormal curve: the change between the last two records nonspecific.

The third electrocardiogram was reported as follows: rate 120; P–R interval shortened and variable; QRS slightly slurred and widened throughout the record; S–T more depressed in 1 to 3, more elevated in $_aV_R$; T inverted in $_aV_L$; S–T more depressed in $_aV_F$ and depressed in V–4 and V–5; A–V nodal tachycardia, with A–V disassociation; horizontal position; definitely abnormal curve, the changes nonspecific.

At necropsy the sclerae were moderately icteric. The abdominal cavity contained 300 to 400 ml. of a clear yellow liquid. The heart was enlarged, weighing 390 gm. There were no grossly discernible abnormalities. The liver weighed 1,980 gm. Its surface was smooth, yellowish-brown, mottled with yellow. The cut surfaces exhibited more or less ill-defined yellowish-red areas of necrosis. The liver consistency was very soft. The kidneys were enlarged, weighing 510 gm., very soft and greenish-yellow in color. On microscopic examination the myocardium showed a very slight increase in connective tissue which was easily noted between the heart muscle fibers. Often the muscle fibers were spread by an edema fluid, which contained lymphocytes and a few polymorphonuclear leukocytes. Scattered throughout, however, were also foci of muscle fiber necrosis with a few infiltrating polymorphonuclear leukocytes, lymphocytes and myocardial reticulocytes. Sometimes a few necrotic muscle fibers were encountered close to foci of, or surrounded by, inflammatory cells, but were not invaded by them. There were also a few necrotic muscle bundles seemingly embedded within healthy fibers. Only the capillaries between some of the necrotic bundles contained a few polymorphonuclear leukocytes and monocytes. There were no hemorrhages. The blood vessels showed no significant alterations. (See Figs. 3 and 4.)

In summary: This patient, who apparently developed a fulminating form of viral hepatitis, dying shortly after admission, with definitely abnormal electrocardiographic tracing, also proved to have had myocarditis. The outstanding changes were foci of scattered necrosis of cardiac muscle fibers with acute inflammation.

CASE 4. The fourth patient° was a 6-year-old white male who developed fever and vomiting 2 weeks before admission. About a week and a half before admission his urine darkened and his skin became yellow. The jaundice gradually increased in intensity. Two days before admission he developed a maculopapular rash over his entire body. On admission the child was lethargic and moderately dehydrated. There was marked jaundice. The liver was palpable 5 cm. below the right costal margin. The temperature was 100.6° F. and pulse rate was 140. The urine bilirubin was 4 plus and urine urobilinogen was negative. The serum bilirubin was 51 mg. per 100 ml. and the serum alkaline phosphatase was 6.2 units. On the second day of his hospital admission he developed petechial hemorrhages. During the first 3 days he continued to have a fever and the liver gradually decreased in size. He died on the fifth hospital day.

At necropsy the skin and sclerae were markedly jaundiced. The heart weighed 150 gm., which is considerably larger than normal. The mural endocardium corresponding to the interventricular septum of the left ventricle showed a number of petechial hemorrhages. The liver was smaller than normal and extremely soft, weighing 500 gm. (instead of about 640 gm.). It was of greenish color. On section, a more or less distinct difference between the cut surface of the right and left lobes could be made out. At first glance, the cut surface of the right lobe seemed to show an exaggerated architecture. The central zones were markedly enlarged, more oval or rectangular in shape. This was seemingly the result of necrosis or severe degeneration of adjacent portions of the central veins. The periportal spaces were greenish-yellow and decreased in extent. The cut surface of the left lobe of the liver showed very small central zones with yellowish periportal spaces which seemed normal in size. The bile ducts showed no gross changes. Neither the hepatic artery, the portal vein, nor the hepatic veins disclosed any abnormalities. The bile ducts, including the papilla of Vater, were patent. The kidneys were enlarged, weighing 250 gm. They were soft and dark green. (See Figs. 5, 6 and 7.)

Microscopic sections of the myocardium again disclosed in a number of sections an edematous fluid separating the heart muscle

°We are indebted to Dr. A. Nachman for the use of the clinical record.

Fig. 5.—Note the necrosis of muscle fibers, the edema and principally lymphocytes. Note also involvement of endocardium. × 250. Iron hematoxylin and eosin preparation.

Fig. 6.—Note the inflammatory cells in the region of the bundle of His. There is also severe degeneration of muscle fibers of the bundle. × 350. Iron hematoxylin and eosin preparation.

Fig. 7.—Note the hemorrhage in the bundle of His, the degeneration of muscle bundle and the swelling of the lining endothelial cells of the endocardium with a few inflammatory cells. × 450. Iron hematoxylin and eosin preparation.

fibers. There were also a few inflammatory cells noted, mainly polymorphonuclear leukocytes. Sections which were taken from the interventricular septum corresponding to the left ventricle disclosed extravasation of red blood corpuscles, as was noted grossly. They were more or less confined to the bundle of His which was obviously compressed. However, polymorphonuclear leukocytes, lymphocytes and a few endothelial cells were also seen surrounding individual bundles which showed either marked cloudy swelling or clear-cut necrosis. The lining endocardial cells in certain areas were markedly swollen, and foci of polymorphonuclear leukocytes were noted between them and in the adjacent myocardium. In other fields there were localized accumulations of granulocytes, a few lymphocytes and endothelial leukocytes, intermingled with red blood corpuscles attached to the endocardium and appearing as minute thrombi. There was a diffuse marked cloudy swelling of the muscle fibers.

In summary: In this child with typical liver changes of acute viral hepatitis, a rather severe myocarditis was found. Many changes were confined to the left bundle branch. In addition to outspoken hemorrhages, there was acute inflammation with muscle necrosis. There was also a more diffuse myocarditis.

Discussion. In all of these patients both acute hepatitis and myocarditis were found. Although there is no definite proof that the hepatitis was of viral origin, grossly and microscopically it corresponded to the classical description of Lucké[6] and many others. Clinically, and from the clinical laboratory point of view, these patients were diagnosed as having viral hepatitis. Clinically, myocarditis was suspected in 2 patients because of the electrocardiographic changes. Also the rapid clinical course in three of these patients (Cases 2, 3 and 4) may have led to the assumption of a severe complication. Although 3 of our 4 patients also had an early bronchopneumonia, it is not likely that the myocarditis was caused by whatever had caused the pneumonia, because the bronchopneumonia was obviously a terminal event. In a study on myocarditis complicating pneumonia it was shown that myocarditis usually occurred late in the disease when the lung showed evidence of organization. Besides, the myocarditis had quite characteristic histologic features which are not encountered in that complicating bronchopneumonia[9]. Case 3 also showed evidence of pyemia with abscesses in the myocardium and kidneys. Although the abscesses in the myocardium, or the suppurative myocarditis, were obviously caused by staphylococci, there were also other inflammatory changes in the myocardium which corresponded well to those seen in our other 3 patients, so that it may be assumed that the patient had both lesions in the heart: staphylococcic abscesses and a myocarditis most likely caused by the virus of epidemic hepatitis. In the following only attention to the latter is being given.

The most characteristic feature of the myocarditis was minute foci of necrosis of isolated muscle bundles. These were often surrounded by lymphocytes, myocardial reticulocytes and a few polymorphonuclear leukocytes. However, also minute isolated necrotic muscle fibers not surrounded by inflammatory cells were noted. Most interesting are the isolated muscle fiber necroses involving the left bundle of His with the presence of a few lymphocytes and polymorphonuclear leukocytes, as noted in 3 of our 4 patients. These were discovered since sections were taken through the septum because of the gross hemorrhages. While these also showed the extravasation of red blood corpuscles accompanying the individual bundles, outspoken inflammatory cells with or without red blood corpuscles were found adjacent to the petechiae. The fibers of the bundles could be clearly identified because of

their course parallel to the endocardium, because of their lighter color and because of a moderate amount of edematous connective tissue separating them from the remainder of the myocardium and endocardium. Hemorrhages in that particular area have been found in many instances of jaundice and were also described by Lucké[6]. One of our cases (Case 4) also showed a minute thrombus attached to the endocardium similar to those which have been reported in children to be a source of emboli in myocarditis[10]. However, no embolic phenomena were present.

Also diffuse myocarditis was found characterized principally by an edematous fluid with very few interspersed inflammatory cells. This myocarditis can well be classified as serous myocarditis.

As stated above, there is no definite proof that the myocarditis observed in these patients with viral hepatitis was caused by the same agent as the hepatitis. However, the minute foci of necrosis in the myocardium which were found in all these instances have also been reported in cases of other virus myocarditis[8] and seem quite characteristic.

It is difficult to estimate how much the myocarditis contributed to the death of the patients. Generalized hyperemia and edema were noted in all patients, although the latter may also have been caused by liver failure. However, the short clinical course of 3 of our 4 patients can be explained by the complicating myocarditis. In contrast, the patient who had suppurative myocarditis and seemingly viral myocarditis died on the 21st day of her hospital stay, perhaps indicating that the myocardial involvement here occurred rather late, which is well correlated with the microscopic picture showing only recent changes. While it is, of course, also possible that the patients succumbed to the liver failure, the mere fact that morphologic changes were found in the myocardium and that 3 patients died after a relatively very short course of the disease would indicate that myocarditis was at least contributory to, if not the sole cause of, death.

The purpose of this investigation was to point out the existence of myocarditis in epidemic hepatitis. These 4 cases were found among 6 instances of epidemic hepatitis which came to our observation between the years 1949 to 1955. It would seem that electrocardiographic studies are indicated in every patient with viral hepatitis, as well as with other viral diseases. Unfortunately, such studies were made in only 2 of our 4 patients. If myocarditis is suspected, this complication may be combated by the realization that three types of changes are found in the myocardium, namely, the more diffuse serous inflammation, the foci of necrosis of isolated muscle bundles, and the changes in the bundle of His.

Summary. Among 6 patients dying with acute viral hepatitis there were 4 with acute myocarditis. Three of these patients died after a relatively short course of the disease, 2 with electrocardiographic changes which in retrospect can well be interpreted as having been caused by the myocarditis. The changes in the myocardium were characterized by minute foci of necrosis and a more diffuse serous inflammation. In 3 of these 4 cases the bundle of His was involved, with necrosis of isolated fibers, hemorrhage and an acute inflammatory exudate.

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SUMMARIO IN INTERLINGUA

Myocarditis in (Epidemic) Hepatitis Viral

Inter 6 patientes moriente con acute hepatitis viral, 4 habeva acute myocarditis. Tres de iste patientes moriva post un relativemente breve curso del morbo 2 con alterationes electrocardiographic que in retrospecto pare ben interpretabile como causate per myocarditis. Le alterationes in le myocardio esseva characterisate per minute focos necrotic e un plus diffuse inflammation serose. In 3 del 4 casos, le fasce de His esseva involvite, con necrosis de fibras isolate, hemorrhagia, e un acute exsudato inflammatori.

SUMMARIO IN INTERLINGUA

(See page 140 for original article)

Tractamento a Tartrato de Pentolinium in Casos Ambulatori de Hypertension Un Methodo pro le Regulation del Dosage

Tartrato de pentolinium se provava altemente satisfactori in le reduction del pression sanguinee de 26 patientes con sever o progressive hypertension tractate durante periodos de inter 3 septimanas e 11 menses.

Le droga esseva administrate oralmente tres vices per die, con un dosage total de non plus que 300 mg. Omne administrationes esseva facite un medie hora ante repastos. Reserpina in doses de 0,25 mg esseva administrate immediatemente post le repastos. In omne patientes, reductiones significative (non necessarimente usque a nivellos normal) occurreva in le systolic e diastolic pressiones sanguinee in posituras tanto sedente como etiam jacente.

Le stato cardiac, retinal, e coronari de omne patientes esseva meliorate, si o non le pression sanguinee esseva reducite a nivellos vicin al norma. Un patiente moriva de hemorrhagia cerebral in despecto de un reduction del pression systolic per 36 mm Hg e del pression diastolic per 38 mm Hg.

Le correcte regulation del programma therapeutic resultava in le domination de effectos lateral.

Le meticulose adjustamento del dosage es le plus importante factor individual in le uso de pentolinium. Le action physiologic ganglio-blocante de pentolinium resultante in le interruption del normal reflexo vasoconstrictor compensatori, un action que se manifesta per variationes postural, esseva usate como guida in le determination del dose de election pro le individuo in question.

Observationes del pression sanguinee, facite a non importa qual tempore durante le activitate del droga (amontante a un total de circa 8 horas) per medio del "methodo angular," servi a indicar si le reflexo postural vasoconstrictor es rumpite o ancora intacte e, per consequente, si o non le dose debe esser adjustate.

OBSERVATIONS ON THE SOURCE OF ELEVATED PLASMA AMMONIA LEVELS IN HEPATIC INSUFFICIENCY

By Hyman J. Zimmerman, M.D.
CHIEF, MEDICAL SERVICE AND CLINICAL ASSOCIATE PROFESSOR OF MEDICINE

AND

R. J. Korn, M.D.
ASSISTANT CHIEF, MEDICAL SERVICE AND CLINICAL ASSISTANT PROFESSOR OF MEDICINE

WITH THE TECHNICAL ASSISTANCE OF

H. G. Weinstein, A.B.
BIOCHEMIST, RESEARCH LABORATORY

(From the Department of Medicine, Veterans Administration Hospital, West Side, Chicago, Illinois, and University of Illinois College of Medicine, Chicago, Illinois)

Recent studies by a number of investigators[1-5] have demonstrated increased amounts of ammonia in the blood plasma of patients with hepatic coma. It has been shown that the intestinal contents are the probable source of most of this ammonia, which, in the normal individual, is removed from the portal blood by the liver. Kirk[5] and others[8] have maintained that the inability of the cirrhotic liver to remove ammonia is related to diversion of portal blood into collateral channels which by-pass the liver, rather than to impaired ability of the liver to metabolize the ammonia.

The purpose of the present study was 1) to evaluate further the frequency of apparently disturbed ammonia metabolism in patients with hepatic disease, 2) to attempt to evaluate the role of parenchymal dysfunction in the elevation of plasma ammonia and 3) to determine whether the reported[3] efficacy of certain antibiotics in hepatic coma might be related to a decrease in the production of ammonia in the intestinal lumen. A preliminary report of these results has been presented elsewhere[17].

Methods and Procedures. The plasma ammonia level was determined in the fasting state in 66 patients with cirrhosis, 40 patients with hepatitis and in 16 with hepatic coma. As controls, 60 hospitalized patients without demonstrable hepatic disease, clinically or by liver function studies, were studied. The tolerance to oral ammonium chloride, as reflected in the plasma ammonia levels was determined in 7 patients with cirrhosis, 5 with hepatitis and 5 controls. This procedure consisted of the administration of 6 gm. of ammonium chloride after blood was drawn for the determination of the fasting plasma ammonia level. Levels of plasma ammonia were then determined at 30-minute intervals for 2 hours. In 8 patients with cirrhosis and in 6 controls, a gelatin tolerance test was performed by the oral administration of 100 gm. of gelatin after the determination of the fasting ammonia level. Thereafter, the ammonia level was determined at hourly intervals, for 4 hours. After a control tolerance test chlortetracycline (2 gm. daily) was administered for a period of 72 hours and the gelatin tolerance test repeated. In 5 patients with cirrhosis and in 3 controls, a similar study was performed substituting 50 gm. of glycine for the gelatin.

The plasma ammonia level was serially determined in 35 of the 40 patients with viral hepatitis and in 60 of the 66 patients with cirrhosis. In one cirrhotic patient, who had had a spleno-renal shunt performed, the effect of varying the protein intake and of the

administration of oral antimicrobial agents was observed.

The ammonia levels of heparinized plasma were determined by a modification of the micro-diffusion method of Conway[1]. The interval between the drawing of blood and the introduction of the plasma into the Conway dish was 40 to 60 minutes. Diffusion at 10° C. was allowed to continue for 90 minutes after the addition of alkali (saturated solution potassium carbonate) to the outer portion of the Conway dish, which also contained 0.5 ml. of plasma. One per cent boric acid was placed in the center well. With 1% bromcresol green as the indicator, "back-titration" with standardized hydrochloric acid (approx. .003 normal) was performed. Duplicate values usually agreed within 10%; 80 to 95% of added ammonia could be recovered.

This method determines the amount of nitrogenous alkali diffusible under standard conditions. Presumably this alkali is ammonia whether present as such or in loose combination with other substances. The sources for error in this determination and the need for constancy of conditions have been emphasized by Kirk[5], Sherlock[10,13], McDermott[6,7], Traeger[15] and Mann[8]. Particularly important is the length of the interval between the drawing of blood and the determination of the ammonia[13]. The mean plasma ammonia level of the control group in this study was similar to that reported by Mann and his associates[8] who allowed a comparable interval, while Singh[14], Sherlock[10,13], and McDermott[6,7] have reported lower mean ammonia levels in their normals presumably related to a shorter interval between the collection of blood and its introduction into the Conway units.

Results. The fasting level of ammonia in the control group of patients ranged from 0.44 to 1.50 micrograms per ml. of plasma (Fig. 1, first column). In the 40 patients with hepatitis, approximately two-thirds of the values were within these limits but the remainder exceeded the upper limit of normal. Similarly, the majority of the values in the noncomatose cirrhotic patients were within the limits of the control group, although again, approximately 30% were above the upper limits of normal. In all 16 patients with coma, the levels of plasma ammonia were above the normal limits. In two of these patients a normal level was obtained once during a period of coma. Some of the values in comatose patients, however, were lower than some determinations in noncomatose liver disease. Usually, though not invariably, patients with impending coma had abnormally elevated levels.

In 35 of the 40 patients with viral hepatitis, the fasting plasma ammonia levels were determined serially during the course of the disease. In 17 of these patients one or more determinations during the period of deepest jaundice were found to be elevated. This relationship may be seen in Fig. 2 where the levels of ammonia are shown by weeks in the hospital. The values were consistently normal during convalescence. In Fig. 3 are shown the plasma ammonia levels during the course of viral hepatitis in 3 such patients, illustrating the parallelism with other laboratory evidence of severity.

In 60 patients with cirrhosis there were also serial ammonia levels determined. In general the cirrhotic patients who were most severely ill, with evidence of hepatic insufficiency, were most likely to have elevated ammonia levels. Subsequent clinical and laboratory evidence of improvement was frequently associated with a decrease in the ammonia levels (Fig. 4, patient S.S.). In many patients, however, the levels were consistently normal or fluctuated irregularly (Fig. 4, patient A.F.). In several patients, serial levels could be correlated with the development of hepatic coma. Observations on a patient with postnecrotic cirrhosis who developed an episode of major gastrointestinal bleeding, while in the hospital, are shown in Fig. 5. It may be seen that the plasma ammonia was within normal limits before the episode of hemorrhage, rose sharply within 2 days, at which time profound coma had developed, and returned to normal

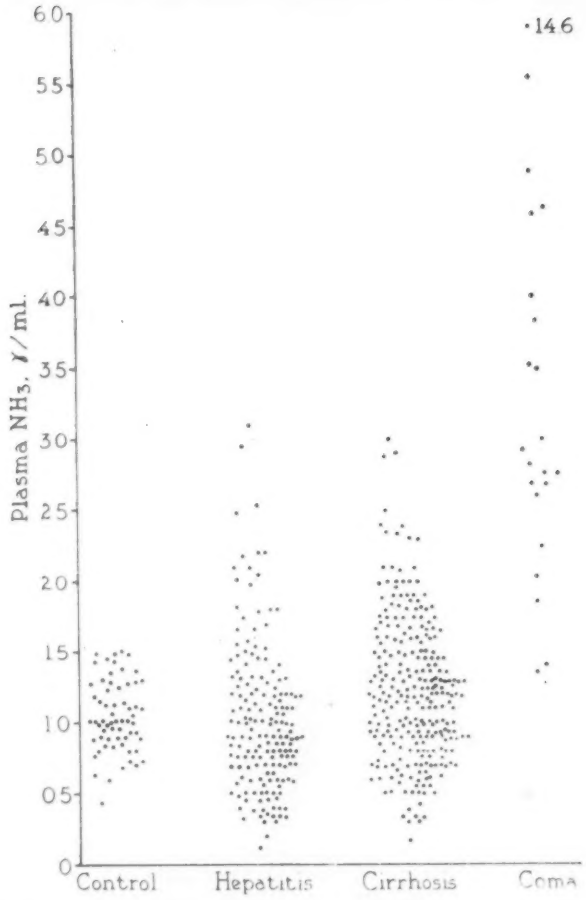

Fig. 1.—Scattergram showing plasma ammonia levels in patients without hepatic disease and in those with hepatitis, cirrhosis and hepatic coma.

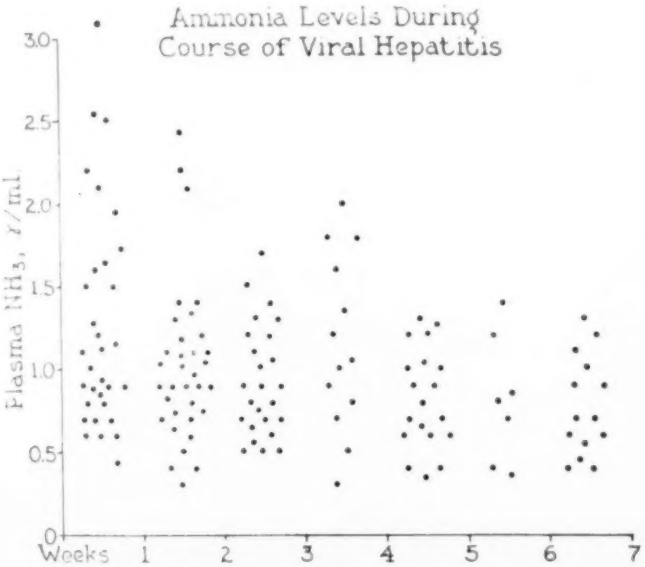

Fig. 2.—Scattergram showing ammonia levels during successive weeks in the hospital in 35 patients with viral hepatitis.

with recovery. The relationship of the decrease in ammonia level to the steroid administration is not clear, although the rapid improvement in the clinical status of the patient was thought to be related to the treatment.

In Fig. 6 are shown the serial plasma ammonia levels in a cirrhotic patient who had had a spleno-renal shunt performed in the past. Periods of agitation, lethargy and stupor were usually, but not invariably associated, with elevation of the ammonia level. A high protein intake was consistently associated with a mounting ammonia level, while a decrease in protein content of the diet was followed by a decreased plasma level of ammonia. The administration of sulfaphthalidine for a period of 2 weeks was not associated with a decrease in the plasma ammonia level. At a later date, observations were made of the plasma ammonia levels during a period of administration of, first, penicillin, then tetracycline (Fig. 6). These antibiotics, given for a pulmonary infection, seemed to be associated with levels of ammonia lower than any seen previously. The significance of this, however, is obscured by the fluctuations in the ammonia level throughout the period of study.

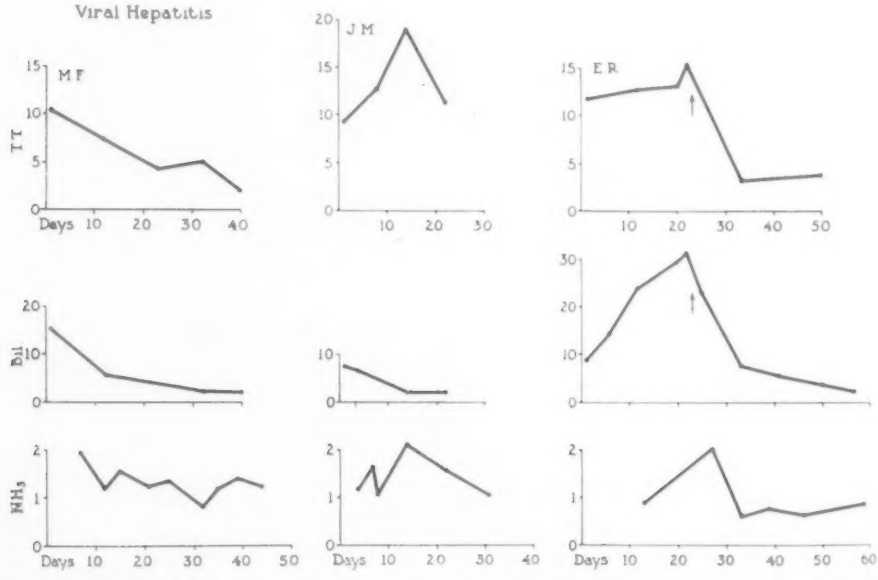

Fig. 3.—Relationship of serial plasma ammonia levels to thymol turbidity (T.T.) and serum bilirubin level (Bil.) in 3 patients with viral hepatitis. Arrow in data of E.R. refers to initiation of ACTH therapy. Please note the prompt fall in thymol turbidity, serum bilirubin and plasma ammonia levels.

The tolerance for ammonium chloride was determined in 4 controls, 7 patients with cirrhosis and 6 with hepatitis. In Fig. 7 are shown the plasma ammonia curves after an oral dose of 6 gm. of ammonium chloride. In the normals the rise was insignificant, while in 5 of the 7 patients with cirrhosis, the plasma ammonia rose to abnormal levels. In the 5 patients with hepa-

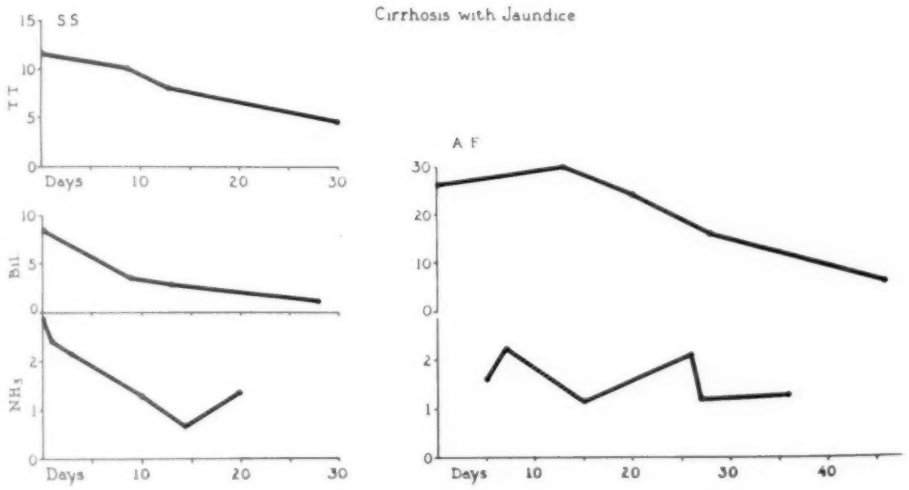

Fig. 4.—Relationship of changes in plasma ammonia level to other laboratory measures of hepatic disease in 2 patients with fatty cirrhosis and jaundice. Please note progressive improvement of plasma ammonia in parallel with improvement in serum bilirubin (Bil.) and thymol turbidity (T.T.) levels in patient S.S. In patient A.F. bilirubin level improved consistently while plasma ammonia level fluctuated irrationally.

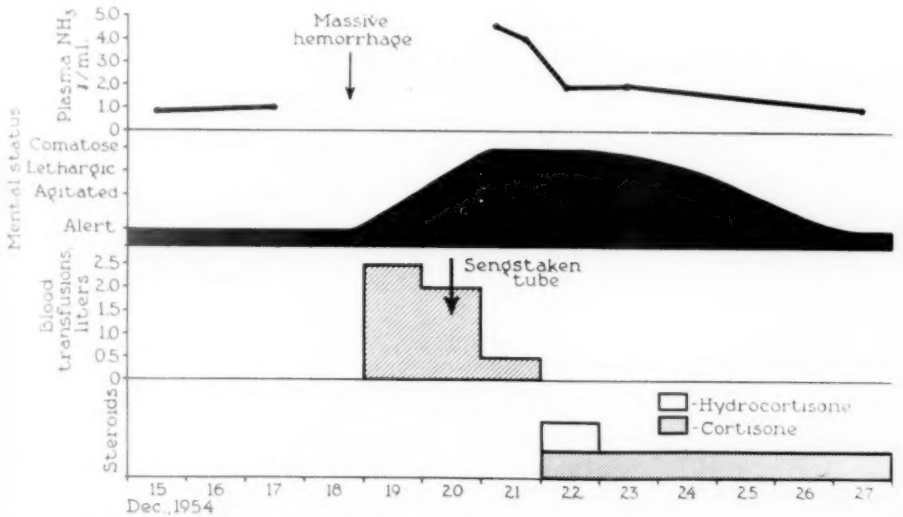

Fig. 5.—Chart illustrating clinical course and plasma ammonia levels in patient E.S., with diagnosis of post-necrotic cirrhosis and portal hypertension. Please note elevated ammonia levels, and profound coma after episode of gastrointestinal hemorrhage.

titis, the ammonia levels did not rise significantly higher than did those of the controls. It should be emphasized, however, that these patients with hepatitis had all passed the most severe phase of the disease.

In Fig. 8 are shown the plasma ammonia levels resulting from the oral administration of 100 gm. of gelatin. After a control determination, chlor-

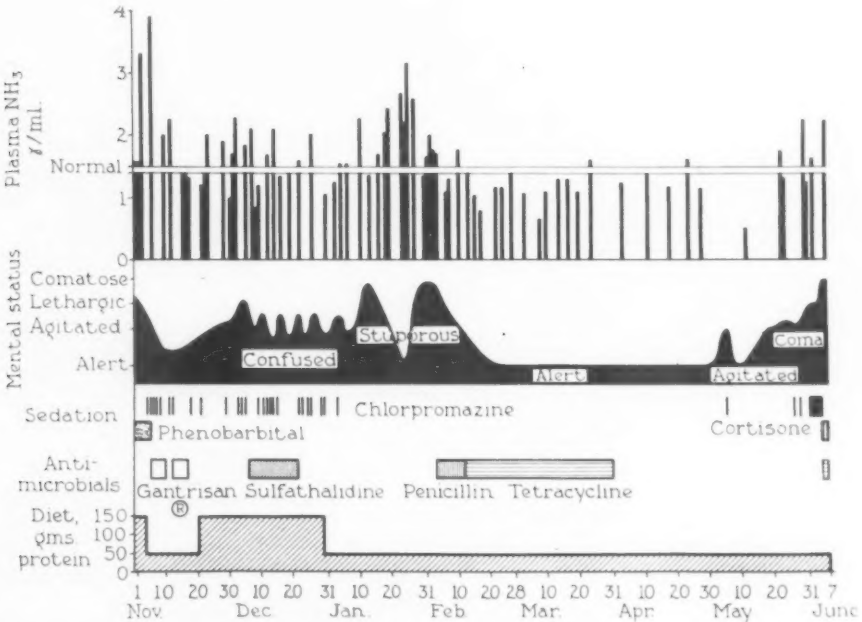

Fig. 6.—Chart illustrating the relationship of plasma ammonia levels to state of consciousness and treatment in patient J.H., with severe cirrhosis. Please note the period of alertness and lowered ammonia levels during a period of tetracycline administration.

tetracycline, 2 gm. daily, was administered orally for 3 days and the "gelatin tolerance test" repeated. As may be seen from Fig. 8, there were moderate elevations of the ammonia levels after this dose of gelatin both in normals and cirrhotics. The administration of chlortetracycline resulted in no significant lessening of the rise of plasma ammonia after the administration of gelatin. Similar results were obtained with the administration of glycine instead of gelatin. Again, the antibiotic did not prevent the slight rise of plasma ammonia following the administration of the glycine.

Discussion. The abnormal levels of plasma ammonia demonstrated in patients with hepatic coma and in some patients with cirrhosis are in agreement with the observations of others[1-8, 10-16]. Abnormal elevation of plasma ammonia in patients with cirrhosis given large oral doses of ammonium chloride has also been previously reported[5,15,16]. Elevated levels during the course of viral hepatitis, observed in the present study, have not been emphasized before.

The concept that elevation of the plasma ammonia level in patients with cirrhosis and in animals[8] or humans[6]

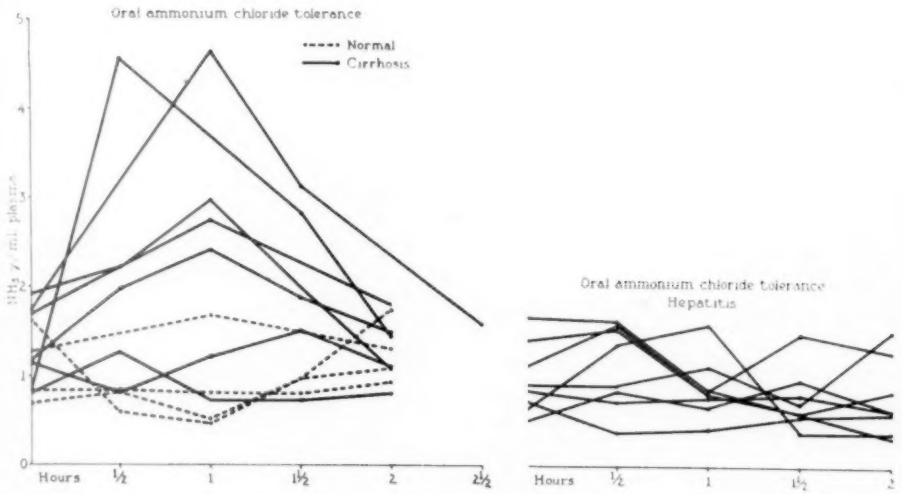

Fig. 7.—Ammonium chloride tolerance test in patients with cirrhosis, hepatitis and normals.

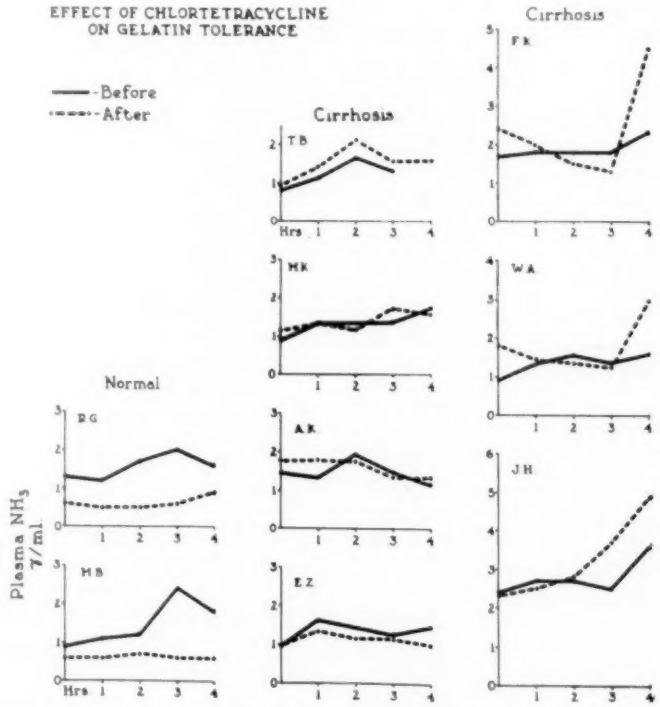

Fig. 8.—Plasma ammonia level response to oral administration of gelatin illustrating lack of significant effect of chlortetracycline.

with Eck fistulae is the result of the passing of the liver via the collateral circulation has been generally accepted[5,15]. The demonstration of elevated ammonia levels during the course of hepatitis raises the possibility that impairment of the ability of the liver to metabolize the ammonia may play a role. Palmer and Brick[9] have recently implied the occurrence of portal hypertension in acute hepatitis by reporting esophageal varices in several patients with this disease. In spite of this evidence the acuteness of the elevation and the parallelism between the elevated ammonia levels and the intensity of the disease are more in keeping with the role of parenchymal dysfunction than with that of liver by-passing in producing the ammonia elevations. Sherlock and her associates[10,13] and McDermott, *et al.*[6,7] have also concluded that hepatic inability to metabolize the ammonia may contribute to the elevated levels. These workers found higher levels of ammonia in the hepatic venous blood than in the peripheral venous blood in patients with severe hepatocellular disease.

It was anticipated that the quantitative aspects of the liberation of ammonia from proteins by intestinal bacteria could be demonstrated by oral administration of gelatin or glycine. The resulting rise of plasma ammonia levels was too slight, however, to fulfill this purpose, and, therefore, to measure the effectiveness of tetracycline drugs in inhibiting the bacterial production of ammonia in the intestine. The observations in patient J. H. (Fig. 6) do suggest that elevated ammonia levels may under some circumstances be depressed by these antibiotics. It has indeed been postulated that the occasional beneficial effect of chlortetracycline in patients with hepatic coma may depend on this mechanism[9,15].

It has recently been reported[2] that the patency of porta-caval shunts may be estimated by the height of the plasma ammonia level after an oral dose of ammonium citrate. Eiseman[2] has stated that the rise of the plasma ammonia level after an oral dose of ammonium citrate is slightly greater in the cirrhotic patient than in the normal, while after a porta-caval shunt the blood ammonia rise resulting from oral ammonium salts is marked and prolonged. The ammonium chloride tolerance curves in 7 cirrhotic patients without porta-caval shunts, reported in the present study, demonstrates that the spontaneous Eck fistulae of advanced cirrhosis may also produce marked elevation of the ammonia tolerance curve. Results similar to ours have been reported by Traeger and his associates[15].

Most observers agree that the correlation between plasma ammonia elevation and hepatic coma is not absolute. Although the plasma of patients in hepatic coma showed ammonia levels above normal, there were many patients with liver disease, not in coma, who had higher levels than some of those who were comatose. While the plasma ammonia level is more consistently relatable to hepatic coma than any other biochemical abnormality of the blood, a consistent role of this aberration in the pathogenesis of coma remains to be proved. Nevertheless, the studies from various clinics support an important role of ammonia in hepatic insufficiency.

Summary and Conclusions. Plasma ammonia levels were found to be elevated in 16 patients with hepatic coma, and in some of a group of noncomatose patients with cirrhosis and hepatitis. In patients with viral hepatitis the elevated levels were noted during the period of greatest intensity of their disease, but not during convalescence. In patients with cirrhosis a correlation

between elevated ammonia levels and coma was demonstrable consistently, and between intensity of disease and elevated levels frequently. Impaired tolerance to ammonium chloride was demonstrated in patients with cirrhosis. Attempts to demonstrate a suppressive effect of tetracycline on intestinal bacterial production of ammonia yielded inconclusive results.

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SUMMARIO IN INTERLINGUA

Observationes Super le Fonte del Elevate Nivellos de Ammoniaco Plasmatic in Insufficientia Hepatic

Elevate nivellos plasmatic de ammoniaco esseva constatate in 16 patientes con coma hepatic e in certe patientes noncomatose suffrente de cirrhosis e hepatitis. In patientes con hepatitis viral le nivellos elevate esseva notate durante le periodo del plus alte intensitate del morbo sed non durante le periodo de convalescentia. In patientes con cirrhosis il esseva possibile demonstrar (a) un correlation de occurrentia uniforme inter elevate nivellos de ammoniaco e coma e (b) un correlation de occurrentia frequente inter le intensitate del morbo e elevate nivellos de ammoniaco. In patientes con cirrhosis un defective toleration pro chlorido de ammonium esseva demonstrate. Resultatos non-conclusive esseva obtenite in le essayo a demonstrar un effecto depressive de tetracyclina super le production de ammoniaco per le bacterios intestinal.

CLINICAL EXPERIENCE WITH ACETYL-DIGITOXIN: PRELIMINARY REPORT*†

By Martin Goldfarb, M.D.
TRAINEE, NATIONAL HEART INSTITUTE, U. S. PUBLIC HEALTH SERVICE, 1954–1955

M. C. Thorner, M.D.
ASSOCIATE CLINICAL PROFESSOR OF MEDICINE

AND

George C. Griffith, M.D.
PROFESSOR OF MEDICINE; COORDINATOR OF CARDIOVASCULAR INSTRUCTION

(From the Department of Medicine [Cardiology], University of Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles, California)

In the constant search toward strengthening our therapeutic armamentarium, even long established drugs are scrutinzed for the possibility of improvement. The disadvantages of the digitalis glycosides are well known to the practitioner. The ideal glycoside would probably be one combining the following properties: 1) Oral administration, 2) rapid digitalizing effect, 3) maintenance for long periods of time with minimal side effects, 4) rapid disappearance of toxic effects upon withholding the drug.

In the search for a product combining these properties, Stoll and Kreis[9] produced acetyl-digitoxin from digitalis lanata by removal of one glucose molecule from Lanatoside A. This differs from digitoxin, which is derived from *Digitalis purpurea*. Rothlin, Bircher, and Schalch[8] have reported that this product is similar to digitoxin in that it is absorbed rapidly and completely from the gastrointestinal tract. This report of Rothlin *et al.* also indicates a decreased toxicity.

This paper summarizes our results in 82 patients receiving acetyl-digitoxin for periods ranging up to 8 months.

Method. Patients selected were those in congestive failure of varying clinical classification and those with uncontrolled atrial fibrillation. Patients were unselected as to age and sex. Some of these patients were switched from another digitalis preparation to acetyl-digitoxin.

These patients were followed clinically by classical signs and symptoms of congestive failure (weight, rales, dyspnea and fatigue, hepatomegaly, edema, venous distention, and the like)[2]. Among laboratory procedures used were blood counts, urinalyses, venous pressures, circulation times (arm-to-tongue), chest films and electrocardiographic tracings.

The drug was given orally in the form of 0.1 mg. and 0.2 mg. tablets.

USES OF ACETYL-DIGITOXIN AS A THERAPEUTIC GLYCOSIDE. A. *Disease states treated.* (See Table 1.)

B. *Initial therapy.* Various digitalizing schedules were tried, depending on the rapidity of action desired. Schedules ranged from a single digitalizing dose to repeated divided doses in pe-

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†Financial assistance kindly furnished by Sandoz Pharmaceuticals, Inc.

Also known as Acylanid, product of Sandoz Pharmaceuticals, Inc.

riods up to 48 hours. Variables included individual patient sensitivity and concomitant therapy at the option of the house staff. This usually included bed rest, diuretics and sodium restriction.

TABLE 1.—DISEASE STATES TREATED

Diagnosis	*Number*
Arteriosclerotic Heart Disease	34
Hypertensive Heart Disease	20
Rheumatic Heart Disease	21
Cor Pulmonale	1
Coronary Artery Disease	5
Luetic Heart Disease	1
Total	82

For purposes of evaluation, initial digitalization results are divided into three general divisions, based on time required for digitalization. These time periods are: 1) a single dose, 2) 12 to 24 hours, and 3) 32 to 48 hours.

The various dosages used and the different time schedules are shown in the following charts:

1. Single dose (See Table 2A).
2. Twelve to 24-hour period (See Table 2B)
3. Thirty-two to 48-hour period (See Table 2C).

TABLE 2A.—INITIAL DIGITALIZATION

Total Dose	*No. of Patients*	*Dosage Schedule*	*Results*
1.8 mg.	2	Single Stat Dose	2, not fully digitalized
2.2 mg.	4	Single Stat Dose	3, fully digitalized 1, fully digitalzed with side effects

TABLE 2B.—INITIAL DIGITALIZATION

Total Dose	*No. of Patients*	*Dosage Schedule*	*Results*
1.2 mg.	3	0.4 mg. q 6 hrs. × 3 doses (18 hours)	1, fully digitalized 1, not fully digitalized 1, not fully digitalized with side effects
1.6 mg.	1	0.8 mg. q 6 hrs. × 2 doses (12 hours)	1, fully digitalized
1.8 mg.	3	0.6 mg. q 4 hrs. × 3 doses (12 hours)	3, fully digitalized
2.4 mg.	6	0.8 mg. q 4 hrs. × 3 doses (12 hours)	3, fully digitalized 3, not fully digitalized

TABLE 2C.—INITIAL DIGITALIZATION

Total Dose	*No. of Patients*	*Dosage Schedule*	*Results*
2.4 mg.	1	0.4 mg. q 8 hrs. × 6 doses (48 hours)	1, fully digitalized
3.2 mg.	1	0.4 mg. q 4 hrs. × 8 doses (32 hours)	1, not fully digitalized
3.2 mg.	12	0.4 mg. q 6 hrs. × 8 doses (48 hours)	7, fully digitalized 2, fully digitalized with side effects 3, not fully digitalized

C. *Maintenance therapy.* The maintenance dose was regulated by clinical evaluation of the patient. Circulation times, venous pressures and daily weighing were also utilized, as indicated, in following the patient. Twenty-nine patients were digitalized and maintained on acetyl-digitoxin. Forty-eight patients were digitalized with other glycosides and switched to maintenance doses of acetyl-digitoxin.

For purposes of evaluation, maintenance results are grouped into three main divisions. These divisions are:

1. Good: even maintenance attained.
2. Fair: dosage occasionally required adjusting.
3. Poor: for varying reasons patient changed to another glycoside for maintenance.

TABLE 3A.—MAINTENANCE RESULTS

Average Daily Maintenance	*No. of Patients*	*Results*
0.1 mg.	28	*GOOD (EVEN MAINTENANCE)*
		14, good
		1, good + occasional side effects
		FAIR (DOSAGE OCCASIONALLY REQUIRED ADJUSTMENT)
		4 fair
		4, fair + occasional side effects
		POOR (CHANGED TO ANOTHER GLYCOSIDE)
		3,failed to maintain compensation
		2, distressing side effects

TABLE 3B.—MAINTENANCE RESULTS

Average Daily Maintenance	*No. of Patients*	*Results*
0.2 mg.	46	*GOOD (EVEN MAINTENANCE)*
		25, good
		5, good + occasional side effects
		FAIR (DOSAGE OCCASIONALLY REQUIRED ADJUSTMENT)
		11, fair
		POOR (CHANGED TO ANOTHER GLYCOSIDE)
		3, failed to maintain compensation
		2, distressing side effects

TABLE 3C.—MAINTENANCE RESULTS

Average Daily Maintenance	*No. of Patients*	*Results*
0.15 mg.	1	1, GOOD
0.3 mg.	2	1, FAIR
		1, POOR, changed to another glycoside because of distressing side effects

The results, according to various dosages used, are summarized in the following charts:

1. Maintenance on 0.1 mg. (See Table 3A).
2. Maintenance on 0.2 mg. (See Table 3B).

3. Maintenance on 0.15 mg. and 0.3 mg. (See Table 3C).

SIDE EFFECTS IN PATIENTS RECEIVING ACETYL-DIGITOXIN. Approximately one-fifth of the patients treated with acetyl-digitoxin showed signs of toxicity. Untoward effects seen were nausea, vomiting, diarrhea, blurred vision, headache, and premature ventricular contractions. Nausea and vomiting usually appeared before the appearance of cardiac irregularities. Also two cases of bigeminal rhythm were seen. All side effects disappeared on decreasing or discontinuing the drug. However, one case of pulsus bigeminy persisted for 9 days following discontinuance of medication. (See Table 4.)

TABLE 4.—SIDE EFFECTS

Side Effects	*No. of Patients*	*Course*
Anorexia	1	Disappeared on reducing drug
Nausea	4	" " " "
Vomiting	1	" " " "
Nausea and Vomiting	2	" " " "
Diarrhea	1	" " " "
Blurring of Vision	1	" " " "
Ventricular Premature Beats	3	" " " "
Paroxysmal Auricular Tachycardia	1	" " " "
Bigeminal Rhythm	1	Disappeared after discontinuing drug, 2 days
	1	Disappeared after discontinuing drug, 9 days

TABLE 5.—RATE OF ELIMINATION OF CARDIAC GLYCOSIDES[1,5,6]

Glycoside	*I.V. Maintenance Dose (mg.)*	*I.V. Digitalizing Dose (mg.)*	*Ratio*	*% Eliminated*
1. Strophosid	0.25	0.5	1:2	50
2. Cedilanid	0.4	2.0	1:5	20
3. Digilanid	0.4	2.0	1:5	20
4. Acetyl-Digitoxin	0.2	1.5	1:7	14
5. Digitoxin	0.15	2.0	1:14	7

PHARMACOLOGY. DeGraff and associates[3,4] and Oettel[7] have calculated the absorption ratio of acetyl-digitoxin by comparing oral and intravenous doses necessary for maintenance of compensation. Based on figures of 0.2 mg. intravenously and 0.3 mg. orally, they have concluded that the intestinal absorption is 67%. It has been shown that the maintenance figures for oral administration of acetyl-digitoxin are between 0.1 mg. and 0.2 mg. According to this method of calculation, the absorption ratio from the alimentary tract would be approximately 100%.

Loeffler and associates[5,6] have attempted to determine the latent period by the effect of acetyl-digitoxin on uncontrolled atrial fibrillation. They have arbitrarily decided that the first effect is evidenced by a reduction of the ventricular rate by 10%. The latent period reported is 10 to 20 minutes for the intravenous preparation and 2 to 4 hours by oral administration.

Several groups have reported the rate of elimination as the ratio between the intravenous digitalizing and intravenous maintenance dose. Table 5 compares the experience with acetyl-

digitoxin and other widely used glycosides[1,5,6].

The usual toxic effects of digitalis glycosides were seen and disappeared on decreasing or discontinuing the drug.

No direct comparison with other digitalis glycosides was attempted in this series. It should be noted that 6 patients with unsatisfactory responses to acetyl-digitoxin were maintained successfully with other glycosides; two with digitoxin, two with digitalis leaf, and three with Gitaligin. One of the patients with bigeminal rhythm was successfully maintained on Gitaligin.

Discussion. A new digitalis glycoside has been isolated in an attempt to find a more efficient product that is easier to control with a greater therapeutic margin. In this report it has been shown that acetyl-digitoxin has received an adequate clinical trial in the wards and clinics of a large general hospital during an 8-month period.

Acetyl-digitoxin has proven to be uncomplicated as to use and predictable in its response. It has been used in patients over a long period of time who were followed only with monthly clinic visits. It reduces heart size and rate, and is well absorbed from the intestinal tract.

Approximately one-fifth of the patients treated showed some signs of toxicity. These toxic signs were readily reversible on decreasing the dose or discontinuing the drug.

Acetyl-digitoxin is indicated in all forms of congestive heart failure, in uncontrolled atrial fibrillation, paroxysmal tachycardia and atrial flutter.

By arbitrary standards, we have classified the results percentage-wise. (See Table 6.)

TABLE 6.—INITIAL DIGITALIZATION

%	*Results*
66	Fully digitalized
33	Not fully digitalized
	Maintenance Results
60	Good
26	Fair
14	Poor

No fatalities due to the drug were noted in this series.

Summary. 1. Acetyl-digitoxin, a new digitalis glycoside, has been prepared from digitalis lanata by removal of one glucose molecule from Lanatoside A. It has been shown to act quickly and be well absorbed from the intestinal tract. It decreases heart size and rate, and produces marked diuresis. Acetyl-digitoxin has maintained patients in a state of cardiac compensation for periods up to 8 months.

2. Approximately one-fifth of the patients receiving this drug displayed side effects. The majority of these disappeared within one to 3 days on decreasing or discontinuing the drug, which is more quickly than disappearance with digitoxin.

3. The question of the comparable efficiency of acetyl-digitoxin and other cardiac glycosides has not been answered by this clinical series. The purpose of this study was to evaluate the clinical effect of acetyl-digitoxin and our experiences have been outlined in the report.

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SUMMARIO IN INTERLINGUA

Experientias Clinic con Acetylo-Digitoxina: Reporto Preliminari

1. Acetylo-digitoxina es un nove glycosido de digitalis que es preparate ab *Digitalis lanata* per le elimination de un molecula de glucosa ex lanatosido-A. Su effecto es demonstratemente rapide e illo es ben absorbite per le tubo intestinal. Illo reduce le dimensiones del corde e le frequentia cardiac. Illo produce un marcate diurese. Acetylo-digitoxina ha mantenite patientes in stato de compensation cardiac durante periodos de usque a 8 menses.

2. Circa un quinto del patientes recipiente iste droga exhibiva effectos lateral. Le majoritate de illos dispareva intra periodos de 1 a 3 dies post que le uso del droga esseva reducite o discontinuate. Isto es plus rapide que le disparition del effectos lateral de digitoxina.

3. Le studio del presente serie clinic non resolve le question del efficacia comparative de acetylo-digitoxina e altere glycosidos cardiac. Le objectivo del studio esseva evalutar le effecto clinic de acetylo-digitoxina. Nostre experientias es delineate in nostre reporto.

SUMMARIO IN INTERLINGUA

(See page 155 for original article)

Le Signification Diagnostic de Alterationes de Cholesterol in Stato Libere, Esterificate, e Ligate a Proteina e de Lipo- e Glyco-Proteinas in Lymphoma e Multiple Myeloma

1. Un simple technica ha rendite possibile le studio del mobilitate electrophoretic de cholesterol ligate a proteina in individuos normal e in patientes con lymphoma e myeloma multiple. Iste studios esseva extendite a coperir le analyse del conducta electrophoretic del lipo- e glyco-proteinas in le duo morbos mentionate.

2. In lymphoma, valores total de cholesterol e de esteres de cholesterol es frappante- e characteristicamente reducite in recidiva; illos tende a reverter a nivellos normal in remission. Cholesterol ligate a proteina es augmentate in le fractiones de albumina e globulina alpha e reducite in le fractiones de globulina beta in patientes con le morbo in su phase active. Lipoproteinas e glycoproteinas seque un curso comparabile sed in un forma minus frappante e minus predicibile. Alterationes de cholesterol libere, esterificate, e ligate a proteina es satis characteristic de lymphoma e se trova quasi exclusivemente in stadios avantiate del morbo. Illos non resulta simplemente de anormalitates in le distribution del le alterationes del proteinas seral es simile a illos observate in lymphoma.

3. In myeloma multiple, le nivello total del cholesterol seral es normal. Le distribution del cholesterol inter le fractiones proteinic es normal. Le lipoproteinas e glycoproteinas se associa preferentialmente con le pathologicamente augmentate fractiones proteinic. Simile alterationes occurre in morbo hepatic.

STUDIES ON ELORINE SULFATE, AN ANTICHOLINERGIC DRUG*

By William H. Bachrach, M.D.

and

Herbert Schapiro, M.S.

(From the Veterans Administration Center, Los Angeles, and the Department of Physiology, School of Medicine, University of Southern California, Los Angeles, California)

The purpose of this paper is to report our observations on an anticholinergic drug, Elorine Sulfate, (1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol methylsulfate) which was administered to some 150 individuals in the course of an investigation of its physiological and clinical characteristics.

Methods. A. laboratory studies. (1) *Effect on motility.* Elorine Sulfate was administered orally and parenterally to 20 subjects with balloon tubes in place at various levels of the gastrointestinal tract. Motor activity was recorded by a multi-channel oscillograph. When no spontaneous contractions were observed during the control period, motility was induced by administration of parasympathomimetic drugs or by opiates.

(2) *Effect on gastric secretion.* The effect of Elorine Sulfate on the secretion of hydrochloric acid by the stomach was investigated in 24 tests on duodenal ulcer patients in the fasting state and in response to food, histamine, and insulin hypoglycemia. The position of the aspirating tube was always verified by fluoroscopy.

In a number of instances the fasting and the food-stimulated secretions were studied at one sitting. The patient received the drug about an hour before intubation in the fasting state and the gastric contents were aspirated continuously for 2 hours. A standard breakfast** was then given and samples of the gastric content obtained at 15-minute intervals thereafter until the stomach was free of food particles. In some instances the drug was given at 3-hour intervals during the secretory test.

The effect of Elorine Sulfate on histamine-stimulated secretion was determined by both the continuous histamine and the double-histamine tests.

When insulin hypoglycemia was used as the test stimulus, Elorine Sulfate was administered parenterally at the onset of the gastric secretory response.

Acidity of the gastric content was determined by measuring the pH with the Beckman glass electrode.

B. clinical observations. The clinical material consisted of 94 patients, including 62 cases of peptic ulcer, 23 cases of functional gastrointestinal disorders, 2 each of post-gastrectomy syndrome, regional ileitis, and ulcerative colitis, and one each of recurrent pancreatitis, hiatus hernia and cardiospasm. All of the patients were ambulatory; 52 were seen in private practice and 42 in the gastrointestinal follow-up clinic of the Veterans Administration Hospital. Ten ulcer patients who were asymptomatic at the outset of this study were given Elorine Sulfate to evaluate its effect in preventing recurrences of ulcer symptoms. In 10 of the patients (7 with functional disorders, one with regional ileitis, one with post-gastrectomy symptoms, and one with hiatus hernia), the drug was given in combination with Amytal.† These 10 cases are not included in the tabulations.

All of the ulcer patients in this series received, in addition to the test drug, some form of diet, and adequate doses of antacids. This plan was followed because previous experience has shown that anticholinergic drugs

*Supported in part by a grant from Eli Lilly & Company, Indianapolis, Indiana.

**Two 4-minute eggs, two slices white toast, two pats butter, 200 ml. milk.

†Co-elorine.

are ineffective as the sole treatment of peptic ulcer.

Response to treatment was classified as *Asymptomatic*, *Incomplete*, or *None*, the definitions of these terms being as follows:

Asymptomatic: Complete disappearance of the symptoms of the ailment for which the patient is primarily being treated. For example, in a patient with pyrosis, belching, and epigastric pain due to a peptic ulcer, and headache due to severe hypertension, the patient is classed as asymptomatic if the ulcer symptoms disappear, even though the headache may persist.

Incomplete: The patient is improved, but some symptoms of the primary ailment remain.

None: No significant improvement.

For oral administration, Elorine Sulfate was available as coated tablets* and as capsules, each in 25 and 50 mg. doses, and for parenteral administration in a solution containing 5 mg. per ml. Patients were generally started on 25 or 50 mg. every 3 or 4 hours, increasing in increments of 25 or 50 mg. per dose until definite side-effects were recorded on a special form devised for this purpose.

Each visit is begun with the following question, always stated in exactly the same words: "What effects have you noticed from your treatment?" Usually, the patient replies with some statement about his symptomatic response. If he makes no mention of side-effects, he is asked, "Anything else?" If he still makes no mention of side-effects, he is then asked specifically about each condition listed in the form. Side-effects elicited by this direct questioning are graded I. If, upon being asked about the effects of treatment, the patient calls attention to certain side-effects, these are graded II to IV according to their severity. The complete scale of grading is as follows:

Grade	*Definition*
0	No side-effects admitted, even when specifically asked.
I	Side-effects admitted only if specifically asked.
II	Side-effects described spontaneously, but not severe enough to require attention.
III	Side-effects described spontaneously, and sufficiently severe to require some attention such as aspirin for headache, chewing gum for xerostomia, laxative for constipation, or reduction in dosage.
IV	Side-effects requiring discontinuance of the drug.

*The tablets are not commercially available.

Results. A. LABORATORY OBSERVATIONS. 1) *Gastrointestinal Motility.* Since at the beginning of this study the effective parenteral dose of Elorine Sulfate in the human had not been established, the drug was injected intravenously with extreme caution in a number of subjects, starting with 0.1 mg. and increasing the amount until there was a clear-cut effect on either the motility or on some other physiological function such as the secretion of saliva or the heart rate. These experiments indicated that a parenteral injection of more than 5 mg. was necessary to obtain appreciable inhibition of motility.

Preliminary orientation to the effective oral dose suggested that by this route, reduction of motility would require single doses in excess of 75 mg. The results of further experiments, directed towards identifying the optimal dosage for inhibition of motility by both parenteral and oral routes, may be summarized as follows:

(a) The intravenous threshold dose for significant inhibition of spontaneous gastrointestinal motility and for motility stimulated by parasympathomimetic drugs is 10 mg. The 5-mg. dose was rarely effective. The optimum dose for complete and prolonged inhibition appears to be 20 mg. At this dose level, the hypertonus of the gut which follows the injection of opiates is counteracted. Elorine Sulfate does not annul spasm of the choledochal sphincter induced by opiates.

(b) The oral antimotility dose appears to be of the order of 200 mg.

2) GASTRIC SECRETION. (a) *Fasting secretion.* A single injection of 10 mg. or more of Elorine Sulfate unequivocally depresses the basal secretion of hydrochloric acid for approximately 2 hours in the duodenal ulcer patient. A 50 mg. oral dose taken one hour before

the intubation appears to have no significant effect. Clear-cut inhibition by oral route does not occur until the dose is increased to 200 mg. (Table 1).

(b) *Food-stimulated secretion.* In 12 experiments, the oral administration of Elorine Sulfate in graded doses up to 250 mg. did not prevent the gastric secretory response to a standard meal.

(c) *Insulin-stimulated secretion.* The gastric acid response to insulin hypoglycemia is neither prevented nor abolished by therapeutic doses of Elorine Sulfate.

(d) *Histamine-stimulated secretion.* A single intravenous injection of 5 mg. of Elorine Sulfate unequivocally reduces the output of acid following histamine (Table 1).

B. CLINICAL OBSERVATIONS (Table 2): Functional dyspepsia appeared relieved by Elorine Sulfate in only one of the 16 patients treated. There was likewise no benefit in cases of pancreatitis, ileitis, colitis, and post-gastrectomy syndrome.

Among the 10 ulcer patients who were free of symptoms when Elorine Sulfate was started, 9 were able to tolerate the drug; 8 of these remained asymptomatic, and one developed a recurrence while on the management.

TABLE 1.—EFFECT OF ELORINE SULFATE ON GASTRIC SECRETION IN PEPTIC ULCER PATIENTS

Patient	*Dose, mg.*	*Route*	*Effect*		
			Acidity	*Volume*	*Side-effects*
Double Histamine Test					
R.K.	5	I.V.	None	—53%	Xerostomia
G.P.	5	I.V.	Inhibited	—83%	Xerostomia
F.S.	5	I.V.	None	—63%	Xerostomia
D.H.	5	I.V.	None	—58%	Xerostomia
C.S.	5	I.V.	None	—75%	Xerostomia
Fasting Secretion					
F.B.	5	S.C.	None	—67% For 1 hour	Xerostomia
J.B.	5	S.C.	Inhibited	—79% For 2 hours	Xerostomia
F.B.	10	S.C.	None	—68% For 2 hours	Xerostomia
L.S.	20	I.M.	None	—84% For 2 hours	Xerostomia
J.L.	200	Oral	Inhibited	—70% For 4 hours	Xerostomia

TABLE 2.—SUMMARY OF RESULTS OF TREATMENT WITH ELORINE SULFATE

Diagnosis	*Number of Patients*	*Clinical Response*		
		Asymptomatic	*Incomplete*	*None*
Peptic ulcer*	62	40**	20†	2
Functional GI disorders	16	1	5	10
Others	6	0	1	5

* Duodenal 53; gastric 6; jejunal 3.

** Eight of these patients were asymptomatic at outset of treatment. They were included in this study in an attempt to evaluate the action of Elorine Sulfate in preventing recurrences.

† Two of these patients were asymptomatic at outset of treatment; however, one of these patients was unable to tolerate the drug, and the recurrence may have been apparent instead of real; therefore, in the following table this case is listed under "Drug stopped because of toxic effects."

Of 52 patients who had symptoms at the onset of treatment, 32 responded with complete disappearance of complaints. Incomplete or no improvement was recorded in 20 patients, approximately half of whom were unable to remain on the medication for one reason or another (Table 3). Thus, the therapeutic results were good in 60% of patients with peptic ulcer, and in an even higher percentage of those who were able to tolerate the drug.

SIDE-EFFECTS (Table 4). Almost all patients receiving Elorine Sulfate experienced dryness of the mouth, but in only a few instances was this of Grade III or IV intensity. In many cases the side-effects at a given dosage level diminished in severity with continued administration of the drug. Persistent side-effects of significant degree occurred in approximately 10% of the patients.

GENERAL, TOXIC, AND LOCAL IRRITATIVE EFFECTS. Toxic, adverse general or adverse local actions differ from side-effects in that they represent an intolerance on the part of the patient, sometimes in the nature of an idiosyncrasy. Such actions occurred in approximately 10% of the group, the most frequent manifestation being nausea (Table 4).

In 9 patients receiving Elorine Sulfate for periods of from 10 to 64 weeks, blood counts remained normal; no disturbance of renal function was observed in the 4 patients in whom urinalyses were done, nor of liver function in the 3 patients tested after the treatment.

In 10 patients, the function of the myocardium as indicated by the electrocardiograph was not altered after the injection of Elorine Sulfate in single doses up to 30 mg.

TOLERANCE. Elorine Sulfate is generally well-tolerated and may be administered with confidence, particularly

TABLE 3.—SUMMARY OF TREATMENT OF PEPTIC ULCER PATIENTS WITH ELORINE SULFATE

Status of Patient at Beginning of Study	*Number of Patients*	*Symptoms Not Completely Controlled*	*Asymptomatic During Treatment*	*Recurred During Treatment*	*Recurred after Treatment Stopped*	*Drug Stopped Because of Toxic Effects*	*Drug Stopped Because of Severe Side-effects*	*Drug Stopped for Other Reasons*
Asymptomatic	10	..	9	1	..	1*	..	..
Symptomatic	32	20	32	2**	5***	3†	3††	7‡

* Severe nausea after each dose.
** One of these patients required surgery.
*** Two of these patients responded to a subsequent course of treatment with the same drug.
† Severe nausea after each dose, 1; "creepy feeling," 1; "intense nervousness," 1.
†† Dysphagia, 2; dysuria with resulting pyuria, 1.
‡ Dissatisfied with progress, 2; complicating symptoms indistinguishable from toxic effects, 2; felt better on omitting the drug, 3.

since any adverse effects which do occur are not serious and subside promptly on withdrawal of the drug. Any symptoms indicating intolerance to the drug will become manifest at the lower dosage level, and if the patient does not show any adverse reaction at the beginning of treatment, it may be predicted that prolonged administration will have no adverse cumulative effect. For instance, 18 patients have taken 100 mg. or more of Elorine Sulfate 4 or 5 times daily for more than 2 months without incident.

Patients who had previously exhibited an intolerance to a natural or synthetic anticholinergic drug generally have the same difficulty with Elorine Sulfate; and conversely, patients who reacted adversely to Elorine Sulfate reacted similarly to other anticholinergic drugs.

DOSAGE. The parenteral dose, as determined by physiologic observations, is 20 mg.

To determine the oral dose, we have analyzed the data on those patients who remained on treatment 30 days or more, on the assumption that any shorter duration indicated an intolerance of some kind or noncooperation with the management. In more than 60% of patients the effective oral therapeutic dose will be 100 mg. or more every 3 or 4 hours (Table 5).

TABLE 4.—TOXIC EFFECTS AND SIGNIFICANT (GRADE III OR IV) SIDE-EFFECTS OF ELORINE SULFATE*

Dose, mg. ½ to 5 x daily	*Number Patients*	*Number with Adverse Effects*		*Effects*
		Toxic Effects	*Side Effects*	
50–75	35	6	1	Nausea (3 pts.), "creepy feeling," nervousness, insomnia, dysuria
100–125	20	0	4	Constipation, xerostomia (2 pts.), dysphagia
150 or more	9	0	1	Xerostomia

* Complete data available for analysis in 64 patients.

TABLE 5.—ORAL DOSAGE OF ELORINE SULFATE

(Dose Which Produces Perceptible Xerostomia)

Dose (mg. of Drug 3 to 5 Times Daily)	*Number of Patients*	*Per Cent*
50–75	15	38
100	15	38
150	7	18
200	1	..
250	1	..

We have found the tablets and capsules equally effective and equally well-tolerated.

Discussion. Physiological studies indicate clearly the extent to which therapeutic doses of Elorine Sulfate may be expected to contribute to the management of peptic ulcer. Since the two main components of the digestive period of gastric secretion, namely, the cephalic phase and the gastric phase, are not significantly affected, the applicability of the drug to the daytime management of the ulcer patient must be based on its antimotility effect,

whereby the action of antacids in the stomach is prolonged and neutralization of acid correspondingly enhanced. The supplementary action of Elorine Sulfate to antacids in controlling gastric acidity has been demonstrated in quantitative studies by Sun and Shay[1].

The reduction of the basal and the histamine-stimulated secretion shows that Elorine Sulfate does have antisecretory effects, and that, in adequate dosage at bedtime, it should help materially to control the all-important night secretion. From our observations the adequate dose for this purpose is 150 to 200 mg. The side-effects which most patients experience with this dose are not so likely to present a problem during sleeping hours. This coincides with the recent observations of Shay *et al.*[2].

The chronic type of ulcer patient which makes up most of our clinical material provides a severe test for any therapy; however, this is the type of case in which a new drug, if it has merit, should demonstrate its advantages. Also, our criteria for good clinical results are undoubtedly strict, but here again, one expects that a new drug should have something more to offer than can be obtained from conventional management. Tested under these conditions, Elorine Sulfate controlled over 60% of the patients in this series. It is possible that if the drug could be administered to all patients in what Shay *et al.*[2] have termed the "optimal effective dose" (OED), better results might be obtained.

Side-effects of some degree, especially xerostomia, will occur at therapeutic doses of the drug, but only infrequently will side-effects be sufficiently troublesome to interfere with the therapeutic program. A real problem is presented, however, by those patients who manifest toxic effects or some other form of intolerance to Elorine Sulfate, because these individuals almost invariably experience the same reaction to other anticholinergic drugs; in such instances, reliance must be placed on neutralization and sedation.

Conclusions. Elorine Sulfate, an anticholinergic drug, inhibits gastrointestinal motility in single doses of 10 to 20 mg. parenterally and 150 to 200 mg. orally. The same doses depress the basal and histamine-stimulated gastric secretion but not the food or insulin-stimulated secretion.

Addition of Elorine Sulfate to a regimen of intensive neutralization gives complete relief of symptoms in 60% of ulcer patients, but does not delay or prevent recurrences after therapy is discontinued.

The clinical dose of Elorine Sulfate is usually 100 mg. or more every 3 or 4 hours. A bedtime dose of 150 to 200 mg. is recommended.

Side-effects are almost invariably present but are only occasionally troublesome at therapeutic doses. Intolerance to the drug because of adverse local or general reaction occurs in about 10% of patients.

Elorine Sulfate is comparable, in its physiological and clinical characteristics, to the natural anticholinergic drugs and the several other synthetic anticholinergics we have investigated.

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METABOLIC AND PATHOLOGIC EFFECTS OF RENIN IN NEPHRECTOMIZED RATS*

By G. M. C. Masson, Ph.D.

F. del Greco, M.D.

A. C. Corcoran, M.D.

and

Irvine H. Page, M.D.

(From the Research Division of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio)

Repeated administration of renin to rats pretreated with salt and adrenal steroids elicits a syndrome associated with severe renal and widespread vascular damage[10,11]. The pathogenesis of this condition is obscure. Relevant facts are: (a) nephrectomy enhances the pressor effect of renin in both dog and rat[14], (b) salt excess enhances the proteinuretic and diuretic effects of renin in the rat[3,13], (c) pretreatment of rats with salt and adrenal steroids increases its pressor effect[14], and (d) in the recently nephrectomized dog, renin elicits necrotizing vascular lesions[12,23]. Hence it seemed likely that salt and steroid pretreatment might sensitize the rat to the vasculotoxic effects of renin by establishing "two conditions, namely hypertension and renal failure, which are known to cause vascular damage"[4,13]. This assumes that salt and steroid might sensitize to renin in such a way that renin would cause a prolonged, nearly total renal ischemia. This situation, if it were established, would have some of the characteristics of nephrectomy, which, in dogs, sensitizes to the vasculotoxic effect of renin[7,23].

This concept was, therefore, tested by studying the vascular and toxic effects of renin in nephrectomized rats, and since the diuresis and proteinuria elicited by renin in intact rats suggest that it alters fluid exchange and vascular permeability, these functions were also examined.

In the first series of experiments, in which drinking fluid was provided to the animals, the results indicated that renin provoked thirst, serous effusions and decreases in bleeding volume. A second series of experiments were done in rats deprived of fluid; these showed that fluid excess was not the cause of the serous effusions. In a third series, we examined the effects of more prolonged renin treatment on mortality and the occurrence of vascular lesions, and, in the last series nephrectomy was done in rats pretreated with desoxycorticosterone or cortisone, with the aim of simulating the possible conditions in salt-steroid-renin disease.

Methods. Male Sprague-Dawley rats were nephrectomized in 2 stages and placed individually in metabolism cages. Food consisted of Purina fox chow. The renin preparation, similar to the one used in previous experiments

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in dogs[12] and rats[10], contained 15 mg. of protein per ml. and its pressor activity was 28 Goldblatt dog units per ml. Among the observations made were: mortality, fluid intake, body weight, bleeding volume (drawing blood from the carotid under ether anesthesia), hematocrit, serum and effusions fluid proteins[8], serum cholesterol[1], urea nitrogen[2] and serum osmolarity (freezing point technique using Fiske osmometer). The osmolarity values of the serum were corrected for urea. In some instances, tissues (heart, intestinal tract, mesentery) were removed and histologically examined following staining with hematoxylin-eosin and periodic acid-fuchsin.

Results. 1. RENIN EFFECTS WITH FREE FLUID INTAKE. Twenty-four male rats weighing 340 to 420 gm. were bilaterally nephrectomized. They were given by groups, water alone (I) or with renin (III) and saline alone (II) or with renin (IV) (Table 1). Renin was administered subcutaneously in a total dose of 21 units, divided in 3 injections over 24 hours, at the end of which time the animals, except 2 of Group IV which had died, were sacrificed by bleeding.

The effects of fluid intake are reflected in changes in body weight, which increased in all rats except those given water alone. Renin decreased bleeding volume and increased hematocrit, while salt alone tended to have similar effects. Serous (pleural and ascitic) effusions were present in all those given saline or renin. Serum urea concentrations were decreased in rats with a positive fluid balance (salt or renin treatment). Serum total protein concentrations and cholesterol were the same in all groups. Serum water non-urea osmolarity was increased in rats given saline and decreased in rats given water and renin.

We have shown elsewhere[16] that renin provokes serous effusions in nephrectomized animals, that the protein patterns of these effusions indicate that they arise as serum transudates, and have concluded that their formation reflects a nephrectomy-potentiated effect of renin on vascular permeability. The above data extend these observations. They show that the thirst induced by renin in nephrectomized rats is not a result of primary stimulation of thirst centers, nor of increased serum non-urea osmolarity. Rather it is due to oligemia consequent on transudate formation. The fact that saline alone provoked some thirst[17] and was associated with serous effusion indicated that the experiments should be repeated in animals deprived of fluid, so that the effects of renin alone could be tested.

2. RENIN WITH FLUID DEPRIVATION. Twenty-four rats were nephrectomized and deprived of water and divided into control and renin-treated groups. Renin was given as in the first series. The data are summarized in Table 2. This again shows the serous-effusion producing effect of renin and its association with decreased bleeding volume. Both groups show the effects of fluid deprivation in (as compared with Series 1 above) weight loss, increased serum urea and osmolarity.

Thus, the factor of increased fluid intake is excluded in the formation of serous effusions in renin-treated, nephrectomized rats.

3. MORTALITY AND VASCULAR LESIONS. Thirty-three rats were nephrectomized, placed in groups as in Series 1 and observed up to 72 hours, or until prior death, with daily renin doses equal to those given in Series 1 and 2. The data, summarized in Table 3, show that renin, particularly in saline-treated rats, elicits increased mortality. Saline alone provoked thirst, which water did not, so that the saline group showed a large weight gain which amounted to 120 gm. at 72 hours. Renin also provoked thirst. The thirst-producing effects of renin and saline were additive.

Detailed necropsy studies were done in this series. Prolongation of treatment, it was felt, should reveal such

TABLE 1.—EFFECTS OF RENIN IN NEPHRECTOMIZED RATS GIVEN WATER OF SALINE

Groups	*Treatment*	*Body Weight Gain in gm.*	*Bleeding Volume in ml.*	*Hematocrit Per Cent*	*Serum Urea mg./100 ml.*	*Serum Proteins gm./L.*	*Pleural Fluid Proteins gm./L.*	*Serum Osmolarity mOsm./L*
I.	Water	−14	14.5	38	282	5.05	..	314
		(−16–+1)	(11.5–19.5)	(35–43)	(235–327)	(4–5.5)		(309–321)
II.	Saline	+10	12	44	265	4.96	2.1	333
		(−5–+45)	(10–16)	(43–46)	(224–301)	(4.5–5.2)	(1.7–2.4)	(325–338)
III.	Water + Renin	+19	9.8	63	260	5.07	2.6	291
		(+12–+22)	(9–11)	(53–68)	(244–272)	(4.6–5.3)	(2.3–3.1)	(286–294)
IV.	Saline + Renin	+18*	8	55	209	5.11	2	331
		(0–+80)	(7–9)	(51–58)	(156–253)	(4.5–6.3)	(1.8–2.2)	(327–335)

* 2 rats died.

TABLE 2.—EFFECTS OF RENIN IN NEPHRECTOMIZED RATS DEPRIVED OF FLUIDS

Treatment	*Body Weight Gain in gm.*	*Bleeding Volume in ml.*	*Serum Urea mg./100 ml.*	*Serum Proteins gm./L.*	*Pleural Fluid Proteins gm./L.*	*Serum Osmolarity mOsm./L.*
0	−20	12.8	405	5.4	..	346
	(−34–−10)	(11–14)	(278–595)	(4.6–6.1)		(318–378)
Renin	−17	7.3	460	5	2.85	348
	(−37–−7)	(2–10)	(378–650)	(3.6–6.2)	(1.8–3.6)	(330–360)

TABLE 3.—TOXICITY OF RENIN IN NEPHRECTOMIZED RATS GIVEN WATER OR SALINE TO DRINK

Treatment	No. of Rats	Mortality at		Fluid Intake at		Body Weight Changes at		
		24 Hours	48 Hours	24 Hours	48 Hours	24 Hours	48 Hours	72 Hours
Water	10	0	0	19 (5–45)	7 (0–15)	+5 (−5–+9)	−17 (−28–+8)	−27 (−44–−3)
Saline	13	0	2	45 (25–80)	53 (5–110)	+39 (+10–+63)	+70 (+40–+150)	+118 (+79–+217)
Water + renin	4	1	3	46 (35–55)	..	+34 (+19–+40)	..	..
Saline + renin	6	4	2	72 (5–150)	..	+48 (0–+99)	..	..

TABLE 4.—EFFECTS OF RENIN, SALT AND NEPHRECTOMY IN RATS PRETREATED WITH DESOXYCORTICOSTERONE AND CORTISONE

Treatment	Body Weight		Fluid Intake		Mortality at	
	A	P	A	P	24 Hours	48 Hours
DCA	162 (144–176)	171 (155–187)	100 (75–140)	25 (10–32)	0	2
DCA + Renin	167 (139–185)	188 (166–211)	96 (25–120)	44 (40–52)	3	3
Cortisone	125 (98–166)	165 (130–215)	50 (25–85)	53 (30–65)	0	4
Cortisone + Renin	125 (95–148)	149 (133–176)	38 (30–52)	54 (42–73)	6	..

NOTE: In the various columns, the values corresponding to *A* and *P* are respectively those obtained for the 24-hour period ante- and post-nephrectomy.

lesions as renin might elicit. However, except for diffuse areas of hemorrhage into the gastrointestinal tract, particularly in the pyloric end of the stomach and proximal small bowel in all groups, and serous effusions in the renin groups, no gross lesions were demonstrable. Microscopically there were occasional focal and minimal hyalinization or necrosis of some arterioles in the areas of hemorrhage. These were faintly demonstrable with the PAS strain; there was no appearance of PAS positive exudate in or around the vessel wall; these minor lesions were equally demonstrable in all groups. As mentioned by Toussaint[22], we noticed some degenerative lesions of muscle fibers particularly in the auricles, consisting of fragmentation of the fibers and calcium deposits.

4. RENIN IN RATS NEPHRECTOMIZED AFTER SALT AND STEROID TREATMENT. The low incidence and minor character of vascular lesions in Series 3 show that nephrectomy as such (actual or, as was supposed might be the case with renin treatment, virtual) is not a sufficient partial cause of the lesions in the renin-salt-steroid disease. However, the steroid as such might be a further factor in this condition, so that experiments were done to examine this possibility.

Rats weighing 100 to 150 gm. were uninephrectomized, placed on 1% NaCl as drink and divided in 4 groups. Animals of Groups I and II were given subcutaneously two 35 mg. DCA implants and those of Group III and IV, 2.5 mg. of cortisone acetate subcutaneously daily. On the 13th day, when all the rats showed increased arterial pressures (range 150 to 220 mm. Hg) the second kidneys were removed and rats of Groups II and IV given renin as above. The results (Table 4) again show the toxic effect of renin. The thirst consequent on saline treatment after nephrectomy is again evident in all groups, although the effect is obscured in the DCA groups by the sharp decrease in intake consequent on cessation of urine formation. The gross lesions at necropsy consisted of anasarca and hemorrhages in heart or intestine, or both, in most animals of all groups. Microscopically, the lesions were similar to those described above in rats not given salt and steroid pretreatment with the exception of one animal in Group I (DCA alone) which showed PAS-positive exudate around myocardial vessels.

These experiments indicate that neither nephrectomy alone nor nephrectomy in the presence of salt or salt and steroid excess adequately accounts for the strong vasculotoxic effects of renin observed in intact or uninephrectomized rats pretreated with salt and steroids.

Discussion. The observations confirm the fact that, in nephrectomized animals, the administration of renin results in serous effusions, independently of fluid intake. This is presumably an aspect of the increase in vascular permeability to proteins which renin and angiotonin elicit[18]; proteinuria is the aspect observed in the intact animal. It is not clear why these effusions should form only after nephrectomy. Nephrectomized animals do not show any more rapid disappearance of tagged plasma protein from the circulation than do intact animals from renin[18]. Perhaps the enhanced and prolonged pressor effect of renin, observed after nephrectomy, provokes a degree of heart failure which would contribute to the formation of effusions.

The deleterious effects of renin in nephrectomized rats seem to result principally from oligemia, transudate formation and possibly from heart failure. It seems very significant that they are not, as in the salt-steroid pretreated

intact or uninephrectomized rat, associated with intense, widespread vascular lesions, although such lesions are observed in nephrectomized dogs given renin[12]. Even when renin is given to nephrectomized rats pretreated with salt and steroid the lesions do not appear. Oligemia, with consequent prevention of hypertension would perhaps explain this absence of lesions. In nephrectomized rats, however, renin does cause prolonged rise in blood pressure so that at least some of the animals should have shown lesions. Hence, in the rat, it seems that the presence of the kidneys is essential to the production by renin of vascular lesions and, as a corollary, that virtual nephrectomy by the renal ischemic action of renin is not an explanation of the vasculotoxic effect of renin in salt-steroid pretreated rats. The fact, that the presence of the kidney seems necessary for the production of severe vascular lesions by renin in the rat, contrasts with the situation in the dog, in which the reverse would seem to be the case.

This is one of two major disparities in response between dogs and rats. The first concerns the relations of adrenal function to hypertensive disease. The rat responds to administration of salt and desoxycorticosterone by hypertension and hypertensive vascular lesions[5,9,19]; administration of renin superimposes a state of acute generalized vascular damage[11]; neither occurs in dogs[20]. In our unpublished observations, 10 adrenalectomized dogs given salt with desoxycorticosterone and cortisone showed, over several weeks, slight increases in arterial pressure[19]; they responded to subcutaneous administrations of renin with moderate further increases of arterial pressure to a level of about 200 mm. Hg, but they did not develop manifest gross or definable microscopic lesions.

The second disparity concerns the effect of nephrectomy. The recently nephrectomized dog responds to renin by a severe toxic state associated with intense vascular damage[12]; if life is prolonged by vividialysis, nephrectomized dogs commonly develop moderate hypertension and, again, intense vascular damage[15]. In contrast, as seen above, renin does not elicit acute vascular damage in recently nephrectomized rats and, while nephrectomized rats maintained by peritoneal dialysis manifest some hypertension, the lesions they develop do not have the characteristics of hypertensive vascular disease[6].

Summary and Conclusions. 1. Renin is deleterious when injected subcutaneously in nephrectomized rats. This effect is independent of fluid intake or pretreatment with salt or adrenal steroids. It is not associated with production of acute blood vessel disease, but is due to formation of serous effusions which deplete plasma volume and stimulate thirst.

2. In uninephrectomized rats pretreated with desoxycorticosterone and salt, renin induces acute vascular disease. The present data indicate that the presence of kidney tissue is essential to the production of these vascular lesions. In this respect, as in the hypertensive properties of salt and adrenal steroids, the rat differs from the dog which latter, after nephrectomy, rapidly develops vascular lesions when renin is given.

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SUMMARIO E CONCLUSIONES IN INTERLINGUA

Effectos Metabolic e Pathologic de Renina in Rattos Nephrectomisate

1. Renina es nocive quando injicite subcutaneemente in rattos nephrectomisate. Iste effecto es independente de ingestion de fluido o de pretractamento con sal o steroides adrenal. Illo non es associate con le production de acute morbo vascular sed resulta del formation de effusiones serose que reduce le volumine plasmatic e stimula sete.

2. In mononephrectomisate rattos pretractate con disoxycorticosterona e sal, renina causa acute morbo vascular. Le datos hic colligite indica que le presentia de texito renal es necessari in le production de tal lesiones vascular. In iste respecto, como relative al qualitates hypertensive de sal e de steroides adrenal, le ratto differe del can. Isto disveloppa rapidemente lesiones vascular quando renina es administrate post nephrectomia.

THE EFFECT OF ESTROGEN THERAPY ON PATIENTS WITH ANGINA PECTORIS

By Billy B. Oliver, M.D.

and

Ben Friedman, M.D.

(From the Medical Service of the Veterans Administration Hospital, McKinney, Texas, and the University of Texas Southwestern Medical School, Dallas, Texas)

Recent reports on the favorable effect of estrogens on the experimentally induced atheromata in the coronary vessels in cockerels[5] and of its action in reversing the abnormal lipoprotein pattern in human subjects[1] have prompted an investigation of its effect on the symptoms and course in patients with arteriosclerotic coronary disease. The present report deals with 17 patients with angina pectoris who were observed closely over a period of 12 to 18 months during which estrogen and placebo therapy was alternately employed. Five additional subjects died during the course of the study.

Procedure. All seventeen individuals, aged 43 to 65 years, had unequivocal angina pectoris. Fifteen of them had suffered one or more myocardial infarctions. When the purpose of the study was explained to them, they were told that two types of female hormones would be used to determine which had the better effect on their pain. They were also told that it was possible that neither drug would help them. The two medications consisted of .05 mg. tablets of ethinyl estradiol and of placebos of identical size, shape, and appearance.* Although the procedure began as a double blind test in which neither patient nor examiner was aware of the type of medication, it could not be so considered in the strict sense since the nature of the side reactions soon identified the variety of therapy with abundant clarity.

The patients were instructed in the use of a diary sheet similar to the one employed by Greiner, Gold, *et al.*[3], in the evaluation of Khellin. The diary contained spaces for daily recording of changes in weather, activity, frequency and severity of anginal pain, number of nitroglycerin tablets used, and for miscellaneous remarks such as unusual stress, reactions, and the like. In addition, each patient was asked periodically to test and record his exercise tolerance by walking over the same ground at a fixed pace and time after meals and noting the distance travelled before the first sign of discomfort.

Subjects returned at intervals of 4 to 8 weeks, at which time the history was reviewed and a physical examination was performed. Periodic determinations carried out included serum cholesterol[2] and phospholipid[8], teleoroentgenograms, electrocardiograms, and Dock displacement ballistocardiograms.

Most patients received .05 mg. of Estinyl four times a day for 3 to 4 months, but then, because of the marked side effects, it usually became necessary to reduce this dosage frequency to twice a day for the remainder of their treatment period. Concomitant administration of 25 mg. of methyl testosterone daily to six of the patients for a period of 2 to 3 weeks failed to prevent these side effects.

No special diet was used in any of the patients and no significant weight change occurred. If the patient was taking antihypertensive agents, digitalis, or pentaerythritol tetranitrate at the beginning of the study, this medication was continued throughout the period of observation.

The 17 subjects were divided into three groups according to the therapeutic order of procedure used: In Group I, estrogen preceded placebo therapy; Group II, placebo preceded estrogen; Group III, estrogen trial between two placebo periods. All patients had at least two weeks of a control period of observation before any pills were administered.

*We are indebted to the Schering Company for furnishing the tablets.

Results. The evaluation of the course that the angina followed during each period was usually based on unidirectional changes in diary, average daily number of nitroglycerin pills, exercise tolerance distance for angina, and the patient's own historical evaluation of his angina as recorded by us at each follow-up visit. In using the above four factors, the emphasis given to each factor was in the order listed above. This emphasis was based on our judgment of the reliability of each factor as a gauge for measuring the course of the

TABLE 1.—EVALUATION OF SEVERITY OF ANGINA PECTORIS ACCORDING TO THERAPY PERIOD

Group Number	*Better on Estrogen Than on Placebo*	*Estrogen Equals Placebo Effect*	*Better on Placebo Than on Estrogen*	*Evaluation Questionable*
I A	..	..	O.B.	..
	..	..	J.B.M.	..
	..	..	B.K.P.	..
	..	..	E.M.	..
	..	..	L.K.J.	..
I B	..	..	B.H.	..
	..	..	S.L.A.	..
I C	..	..	V.L.B.	..
I D	O.W.	..	..	O.W.
II A	..	..	G.F.	..
	..	..	J.E.	..
II B	E.S.	..	..	..
	E.W.L.	..	..	..
	O.C.	..	..	..
II C	..	S.F.W.	..	S.F.W.
III	..	..	S.T.D.	..
	..	F.M.B.	..	F.M.B.

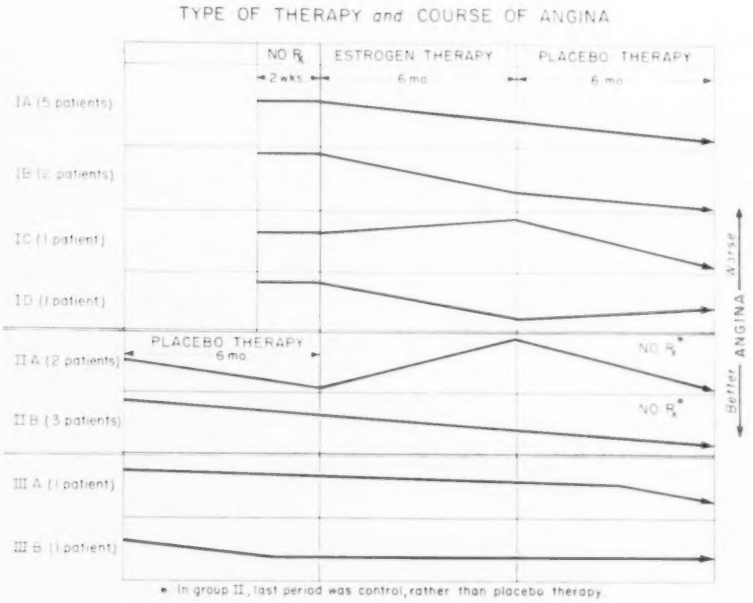

Fig. 1.

angina. For instance in one patient (O.W., Table 2) the data from these four means of evaluation of angina were conflicting. In such an instance most importance was placed on the data from the diary and the daily number of nitroglycerin pills used. However, since these data conflicted with those from his measured exercise tolerance distance and our recordings of his historical evaluation of the angina, then our evaluation of his course was considered of questionable accuracy. The directional changes based on the four criteria employed for evaluation tallied in the vast majority of the 17 subjects. The over-all results in all patients are summarized in Table 1.

graph line I B. There was one patient (Table 5, graph line I C) whose pain seemed to worsen rapidly while he was on estrogen therapy. Then he gradually improved while on placebo therapy. The evaluation of the course of the angina of subject O.W. has been discussed. The data in his case are shown in Table 2 and graph line I D.

In Group II there were 6 individuals who received placebo therapy first, followed later by estrogen therapy. Two of these patients were better during placebo therapy. Their course is represented in the chart of G.F. (Table 6) and by graph line II A. There were 3 subjects whose angina was better while receiving estrogen therapy. Their

TABLE 2.

	Angina by Diary					
Patient O.W.	*Days of Less Total Days*	*Days of None Total Days*	*Angina by History*	*Angina by Exercise Tolerance*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
Control period (14 days)	28%	14%	Same	..	2.3/day	Same
Estrogen period (148 days) .	46%	28%	Worse	5 blocks	.73/day	Worse
Placebo period (240 days) . .	50%	7%	Same to better	8 blocks	1.6/day	Same to better

The three therapeutic groups were further subdivided in Table 1 into lettered groups according to the course of their angina. The fluctuations in the course of angina of each group is recorded in Fig. 1. In Group I there were 5 patients (I A) who showed a rather gradual improvement throughout the study. The chart of O.B. (Table 3) is representative of this group. The graph line I A depicts the rate of decline of angina in them. There were 2 patients whose greatest rate of improvement in anginal pain was during the estrogen period, though the improvement continued at a slower pace during the placebo period. The course is shown in the chart of B.H. (Table 4) and in

course is typified in the chart of E.S. (Table 7) and by graph line II B. It can be easily seen that these individuals showed a gradual improvement throughout all periods of observation. A sixth subject (S.F.W.) developed thrombosis in a small artery of the right leg at the beginning of the placebo period. The consequent severe claudication so hindered his activity that he had practically no angina from then on.

The two Group III patients had a period of estrogen therapy in between two trials of placebo medication. Patient S.T.D. showed gradual improvement throughout the period of observation, the greatest rate of improve-

ment occurring when Serpasil was added to his antihypertensive regimen of C_6 and Apresoline during the last placebo period. His course is represented graphically by line III A. The other individual, F.M.B., was discovered to have very few true anginal pains, but mainly palpitation and muscular skeletal pains. This was discovered during the latter part of the first placebo period. When he was able to definitely discriminate the true anginal pains, they were found to occur so infrequently that his course was very good from then on, but of no value to the study. (See graph line III B.)

TABLE 3.

Patient O.B.	*Angina by Diary* — *Days of More / Total Days*	*Angina by Diary* — *Days of Less / Total Days*	*Angina by History*	*Angina by Exercise Tolerance*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
Control (14 days)	20%	13.3%	2 to 3 times weekly	3 to 5 blocks	1/day	Same
Estrogen (First 3 months)	10.7%	48.8%	6 to 7 times weekly	3 to 5 blocks	.64/day	Same
Estrogen (Last 2 months)	19%	78.6%	2 to 3 times weekly	Too weak to walk enough to tell	.39/day	Markedly decreased, partly due to hot weeks
Placebo period (260 days)	9%	76%	0 to 2 times weekly	6 to 10 blocks	.25/day	Same as before starting estrogen

TABLE 4.

Patient B.H.	*Angina by Diary* * *Days of Some / Total Days*	*Angina by History*	*Exercise Tolerance for Angina*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
Control period (28 days)	82%	Same	1 to 1.5 blocks	.71/day	So-so
Estrogen period (135 days)	17%	Slightly better	1 to 2 blocks	.23/day	Poor
Placebo period (98 days)	17%	Best but no dramatic change	2 to 2.5 blocks	.27/day	Better

* Days of some angina includes all days marked as same, more, or less.

TABLE 5.

Patient V.L.B.	*Angina by Diary* — *Days of More / Total Days*	*Angina by Diary* — *Days of Less / Total Days*	*Angina by History*	*Angina by Exercise Tolerance*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
Control period (14 days)	14%	0%	Same	½ block	4.5/day	Poor
Estrogen period (142 days)	57%	0%	Same	½ block	6/day	Poor
Placebo period (333 days)	57%	22%	Better	3 blocks	4.6/day	Better

There were 5 deaths during the study. Three of these patients had been receiving placebo pills for a period of 2 to 6 weeks when they died suddenly. The other two subjects had been receiving 0.2 mg. ethinyl estradiol for 3 months and 3 weeks, respectively, before they died. Individual C.H. had estrogen therapy. Necropsy revealed that he died from pulmonary infarcts and heart failure rather than a new myocardial infarct.

All of the subjects suffered from rather severe side effects while they were taking estrogens. In 3 or 4 of them these side effects were insidious,

TABLE 6.

Patient G.F.	*Angina by Diary* — *Days of Some Total Days*	*Angina by Diary* — *Days of More Total Days*	*Angina by History*	*Angina by Exercise Tolerance*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
Control period	Through patient's misunderstanding he did not keep diary					
Placebo period						
1. First 6 months.	52%	7.5%	Same			Fair
2. Last 2 months	5%	5%	Better	3 blocks	.7	Fair
Estrogen period						
1. First 4 months.	95%	43%	Perhaps slightly	¼ block	..	Complained bitterly of
2. Last 2 months	22%	18%	worse than during placebo period	2 to 3 blocks	5.0	fatigue
Last control	2.8%	2.8%	Much better	3 to 4 blocks	1.9	Fair

TABLE 7.

Patient E.S.	*Angina by Diary Days of Some/Total Days*	*Angina by History*	*Exercise Tolerance for Angina*	*Average No. of N.G. Tablets Daily*	*Sense of Well-being and Strength and Energy*
First control (14 days)	29%	Same	Not measured	.27/day	Fair
Placebo period (199 days)	13%	Slight but definite improvement	6 to 7 blocks	.12/day	Good
Estrogen period (153 days)	9.15%	About same as placebo period	6 to 7 blocks	.102/day	Rather poor
Last control (184 days)	7%	Much better than ever	15 blocks	.09/day	Good

taken estrogen daily for 3 months when he developed prolonged pain and died at home. The patient who died after 6 weeks of estrogen therapy had been having more angina, more weakness and dyspnea, and gradually increasing heart size while receiving placebo therapy. This downhill course seemed to increase in rate when he was placed on

so that it was not realized how severe they were until the drug was discontinued and a return to the normal state ensued. The most serious of these side effects was not the loss of libido or breast enlargement that occurred in all patients, but the marked fatigue and loss of sense of well-being that developed. On many occasions during estrogen

therapy the patient's diary would indicate less frequent angina, but on questioning him it would be found that he felt much worse. He would then explain that the angina seemed better only because he hadn't the strength or energy to move about enough to provoke pain. The loss of libido occurred in 2 to 6 weeks. Usually the libido returned in 10 to 14 days after discontinuing estrogen, but in some patients this symptom persisted for many months. The breast enlargement and fatigue were most noticeable after 2 to 3 months of estrogen therapy. The breast enlargement receded very gradually when the drug was withdrawn, but the sense of well-being returned in 10 to 14 days. None of these symptoms was relieved by the administration of 25 mg. of methyl testosterone daily for 2 to 3 weeks in the 6 individuals in whom this was tried. No weight change occurred as a result of the estrogen therapy. Three out of the 4 subjects with very mild hypertension had a very slight lowering of the average systolic diastolic blood pressures during estrogen administration. (The greatest diastolic decline was 5 mm. Hg.) The one patient who had congestive heart failure had no worsening of the heart failure as a result of estrogen administration. Of the 15 subjects in whom sufficient numbers of blood samples were analyzed for total cholesterol and phospholipid, 10 showed a decline in the plasma cholesterol to phospholipid ratio usually as a result of a slight lowering of the total cholesterol and a slight increase in phospholipid concentration[8]. The average decrease in this ratio in all patients was from 310/276 during placebo administration to 291/299 during estrogen therapy. The few electrocardiographic and ballistocardiographic changes that occurred did not add significantly to what was already noted clinically by history, physical examination, and diary.

Interpretation of Results. It will be noted by the courses charted in the graphs that all subjects who completed the study were better at the end than they were at the beginning of the study. We interpret this as a reflection of the beneficial psychogenic effect of the doctor's special interest in a patient. It is safe to say that no dramatically beneficial effects on the angina pectoris were produced by the dosage of estrogen administered here.

The authors believe that the one important finding that has come from this study is that relatively small doses of estrogens produce such serious side effects in men so as to make its use impractical in the treatment of atherosclerotic heart disease. The estrogen dosage employed in this study has been demonstrated to be the minimum effective quantity in reducing the serum cholesterol to phospholipid ratio in the male[4].

Discussion. The pathological studies of Rivin and Dimitroff[6] strongly suggest that large daily estrogen dosage will decrease the severity of coronary atherosclerosis in men. We believe, however, that estrogens will not be used extensively in the treatment of coronary atherosclerosis, since the consequences of the therapy appear to be worse than the immediate manifestations of the disease. The side effect of estrogen therapy is not only temporary loss of sexual function, but the more drastic result is the incapacitating weakness, lassitude, and loss of sense of well-being. These last symptoms may be due to estrogenic antagonism to endogenous testosterone rather than to a specific tissue effect of the estrogens. The nature of the mechanism of production of this side effect by the estrogens is not yet established. A recent

study[7] of more strenuous but more brief estrogen therapy in patients similar to these has emphasized blood lipid changes. These authors also stress the severity of the side effects in their subjects.

Summary. A short term placebo-controlled study has been made of the effect of estrogens on the clinical course of patients with angina pectoris. No definite beneficial or detrimental effect on the angina was demonstrated under the conditions of this study. Our observations on the side effects of estrogen therapy lead us to believe that its use will be impractical in the treatment of atherosclerotic heart disease in the male subject.

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SUMMARIO IN INTERLINGUA

Effecto de Therapia a Estrogeno Super Patientes con Angina de Pectore

Esseva executate un studio a breve durantia, controlate per administration de medication fictive, del effecto de estrogenos super le curso clinic de patientes con angina de pectore. Sub le conditiones de iste studio, nulle benefic o nocive effecto super le angina esseva demonstrabile. Nostre observationes del effectos lateral de therapia a estrogeno impone le conclusion que illo non es practicabile in le tractamento de atherosclerotic morbo cardiac in masculos.

CONCLUSIONES IN INTERLINGUA

(See page 192 for original article)

Studios de Elorino-Sulfato, un Droga Anticholinergic

Elorino-Sulfato, un droga anticholinergic, inhibi le motilitate gastrointestinal in doses unic de 10 a 20 mg si administrate parenteralmente, e in doses unic de 150 a 200 mg si administrate oralmente. Le mesme doses deprime le gastro-secretion basal e histamino-stimulate sed non le secretion stimulate per alimentos o illo stimulate per insulina.

Le addition de Elorino-Sulfato a un regime de intense neutralisation resulta in un complete alleviamento del symptomas in 60 pro cento del patientes de ulcere sed non retarda o preveni recurrentias post que le therapia es discontinuate.

Le dose clinic de Elorino-Sulfato es usualmente 100 mg o plus a intervallos de 3 o 4 horas. Un dose de 150 o 200 mg al hora de dormir es a recommendar.

Effectos lateral se manifesta quasi invariabilemente. Con doses therapeutic illos es rarmente serie. Nontoleration del droga, manifeste in reactiones local o general, occurre in circa 10 pro cento del patientes.

In su characteristicas physiologic e clinic, Elorino-Sulfato es comparabile al drogas anticholinergic natural e plure altere anticholinergicos que nos ha investigate.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.

JOHN RHEA BARTON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

AND

C. G. JOHNSTON, M.S., M.D.

PROFESSOR OF SURGERY, WAYNE UNIVERSITY
DETROIT, MICHIGAN

BLADDER "SUBSTITUTES"

BY JOHN J. MURPHY, M.D.

ASSOCIATE IN UROLOGIC SURGERY, UNIVERSITY OF PENNSYLVANIA

(From the Harrison Department of Surgical Research, Schools of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania)

IN the late nineteenth and early twentieth centuries, a wave of interest in methods of urinary diversion resulted in the development of a number of ingenious operative procedures intended to provide a substitute for the urinary bladder. Almost every conceivable variation in the use of bowel as a reservoir for urine was described. The exhaustive critical review in 1936 of Hinman and Weyrauch[34] discusses each recorded method and groups them according to surgical principles involved. Some of the more interesting procedures are worthy of mention, especially since many of them have been revived and modified in recent years.

CONSTRUCTION OF THE RESERVOIR. The rectum, having natural reservoir properties, was utilized in a number of ways. Mauclaire, in 1895, described implantation of the ureters into the rectum after proximal sigmoid colostomy. Gersuny (1898) attempted to provide continence for the colostomy after a similar procedure by drawing this stoma through the anal sphincter anterior to the rectum. The isolated rectum was anastomosed to the urethra after implantation of the ureters by Lemoine (1912). Berg, in 1907, used an isolated segment of ileum as a urinary conduit to the intact sigmoid colon.

The capacious cecum provided a urinary reservoir for Verhoogen (1908), who isolated this portion of the large bowel, implanted the ureters, and used the appendix as a conduit to the abdominal skin.

A small bowel conduit was described by Cuneo in 1911. He isolated a segment of ileum, closed the proximal

end, and after implantation of the ureters, brought the distal end through the anal sphincter.

The success of these early attempts at "artificial bladder" construction is summarized succinctly by Hinman[33] in his magnificent review (1939). He called them "nothing more than elaborate devices for urinary stagnation." Despite the fundamental truth contained in this statement, attempts to find a satisfactory reservoir for urine, of the types described above, have continued.

Further experimental studies of the procedure described by Lemoine have been reported by Bisgard[5,6] and Rubin[52]. There has been no clinical experience reported with this method.

Modifications of the method of Verhoogen have been reported by Bricker and Eiseman[9], and Gilchrist and Mericks[28,43]. These investigators used the terminal ileum as a conduit to the abdominal skin after implantation of the ureters into a reservoir of right colon and cecum. It was hoped that the ileo-cecal valve would provide continence. The effects of back pressure and repeated or continuous catheterization upon the kidneys have resulted in poor general acceptance of this procedure.

The operation reported by Lowsely[39] and Levitsky[38] in which the isolated distal rectum is used as a urinary reservoir and the proximal rectosigmoid stoma is drawn through the anal sphincter, is a modification of the method of Gersuny. It is liable to all the dangers of any reservoir, with special emphasis upon technical difficulties and the effects of intraluminal back pressure.

The novel approach of Shoemaker[53,54], who describes the use of "reversed sero-muscular grafts" made from segments of small intestine, is noteworthy because of its originality. At present, technical difficulties as well as the usual problems of ureteral transplantation render it of little or no clinical value for total bladder replacement.

TECHNIQUES OF URETEROENTEROSTOMY. Early efforts to prevent peritonitis and urinary fistulae after ureteroenterostomy led to the development of a variety of techniques of ureteral implantation. Most of the early procedures appear to be based upon the principle used by Witzel for his gastrostomy. This has been termed the "muscularizing principle" by Hinman[33,34], and was the forerunner of the "tunneling" technique in which a portion of the distal end of the ureter is surrounded by various layers of the bowel into which it is implanted.

Extraperitoneal implantation of the ureters, another method of avoiding peritonitis, was introduced by Bergenheim[4] in 1896. This principle was revived by Cabot[11] in 1931, and recently by Goodwin[30].

Another ingenious modification which stimulated a great deal of investigation, involved employment of the "intact ureter." Implantation of this structure into the bowel wall without entering the bowel lumen was accomplished while the ureter was still in continuity with the bladder. The uretero-enteral fistula was created later by a variety of 'aseptic" techniques. This was intended to provide a more "natural" ureteral insertion in addition to preventing leakage and peritonitis. Winsbury-White[59], Higgins[31], Nesbit[48] and Hinman[32] were among the leading contributors to this method, which has since been discarded because of its needless complexity and failure to accomplish the "natural" insertion.

Recognition of the fact that intraluminal pressure and ascending infection from the reservoir have an adverse effect upon renal function and upon the clinical course of the patient stim-

ulated attempts at reproduction of the normal uretero-vesical junction in ureteroenterostomy.

Transplantation of the intact ureteral orifices was described in 1894 by Maydl[41], who utilized the entire trigone. Bergenheim[4], in 1896, implanted the intact orifices separately. A modification of this has been reported recently by Goodwin[30]. This method has not proved to be entirely successful in preventing infection and renal damage, and is, of course, of no value when the entire bladder must be removed.

Popularized by Mayo[42] and Coffey[12] very early in this century, the various modifications of the "tunnel" type of ureteroenterostomy have been brought through a complex development by Coffey[13-19], Furniss[26,27], Papin[50,51], Hinman[32,33,34], and others. The present status of this technique is best appreciated from the reports of Leadbetter[37], who has combined the submucous tunnel procedure with the direct elliptical anastomosis of Nesbit[49]. Although Leadbetter has reported good results with this method, the general experience is that the procedure leaves something to be desired in the way of upper urinary tract protection.

Prevention of transmission of pressure and infection from the reservoir to the upper urinary tract by creation of a flap over the ureteroenterostomy stoma was first attempted by Vignoni[56] in 1895. He implanted the ureter upon a V-shaped flap fashioned from the anterior rectal wall, which was then tucked into the rectal lumen. This was accomplished only in animals, and apparently failed. Fowler[25], in 1898, attempted to form a flap of mucosa and submucosa which would cover the ureteral orifices when intrarectal pressure increased. According to Hinman[34], this flap failed because of atrophy. The "nipple" technique of Mathisen[40] represents an ingenious modification of this principle. The implanted distal two to three centimeters of ureter is surrounded by a "nipple" made of the full thickness of bowel, and tucked into the bowel lumen. Clinical experience to date with this procedure is small, but sufficient to indicate that it is not the final answer to the problem.

Open transcolonic anastomosis of the ureters to the sigmoid colon as it overlies the sacrum, as devised by Goodwin[29], offers another recent approach to the "valve" problem. This method awaits further evaluation by accurate follow-up reports on patients so treated, but evidence of upper tract damage has been noted in some of these.

PROBLEMS AND COMPLICATIONS. Careful evaluation of results obtained with the many modifications of reservoir and implantation techniques has provided clarification of many problems, but solution of few. Reports of frequent recurrent pyelonephritis, resulting in loss of renal function, emphasize the dangers of obstruction and infection in such preparations[20,21,23,35].

Absorption of urinary constituents has been shown to play a part in the pathogenesis of the electrolyte imbalance so frequently noted after ureteroenterostomy[10,23,24,47,55]. Lapides[36] has demonstrated beautifully the fact that hyperchloremic acidosis in such patients is due to absorption of urinary constituents in the presence of renal tubular damage. Pyelonephritis, often from obstruction and ascending infection, is the most common cause of the tubular damage, although back pressure alone might suffice in some cases.

A summary of the factors apparently inherent in artificial reservoirs and conduits used as bladder substitutes is presented in Table 1. These are the problems which must be solved to make such "substitutes" physiologically feasible. That they may not be impossible of solution is indicated by

the fact that an occasional patient with ureterosigmoidostomy gets along quite well clinically, and maintains apparently normal renal function and pyelographic appearance for many years. It appears that protection of the kidneys from back pressure, ureteral reflux, and ascending infection is the solution. Investigation of new, and modification of old methods of creating a valve at the ureter-"bladder" junction continues and is a commendable line of endeavor.

stomata[3]. The frequent need for indwelling catheters, with leakage, infection, and calculus formation, and the difficulties of management of two stomata place the method in the category of "not desirable," if not "last resort."

Development of a technique utilizing an isolated segment of bowel purely as a conduit for urine by Bricker[7] and Merscheimer[44], in 1950, marked a real advance in the field of "bladder substitution." This method permits anas-

TABLE 1.—FACTORS AFFECTING FUNCTION OF "BLADDER SUBSTITUTES"

1. Obstruction
   a) At site of ureteral transplantation
   b) At outlet of reservoir or conduit
   c) Because of intraluminal pressure of reservoir or conduit
2. Infection
   a) From exterior (tubes, catheters, and the like)
   b) From interior conduit or reservoir
      1) When first established (isolated segments)
      2) Persisting (in reservoir)
      3) Continual (in intact bowel)
3. Absorption
   Dependent upon:
      a) Surface area of conduit or reservoir
      b) Absorbing powers of conduit or reservoir
      c) Intraluminal pressure of conduit or reservoir

PURE CONDUITS: THE ALTERNATIVE. Other investigators, faced with the clinical need for a satisfactory method of permanent urinary diversion, have abandoned the idea of an internal reservoir, and sought methods by which the urine might be conducted physiologically to an external appliance which might provide this function.

Cutaneous ureterostomy, one of the oldest methods of diversion, has been revived, and attempts have been made to overcome its many difficulties. Mechanical improvements in collecting systems[2,58] are of some aid in making the life of patients so treated more tolerable. When feasible, plastic surgical techniques may help to prevent stricture and provide protruding tomosis of the ureters, regardless of length or condition, to an active segment of normal bowel, isolated from the continuity of the gastrointestinal tract, which empties quickly through an adequate cutaneous stoma. Minimal back pressure and excellent drainage of the kidneys result. Absorption of urinary constituents occurs[47], but is of no apparent clinical significance because of the excellent protection afforded the upper urinary tract. A reliable leak-proof adherent bag provides the reservoir function in this so-called bladder "substitute." Clinical experience to date[1,8,45,46,57] emphasizes the renal protection offered by this method of diversion, as well as its reasonable "social convenience."

Although small bowel (terminal ileum) has been used exclusively by Bricker, short isolated segments of sigmoid colon have functioned as well clinically[46], and there is suggestive laboratory evidence that this portion of the bowel may absorb less than others[47]. This may offer an extra margin of safety in regard to protection from electrolyte imbalance. In the course of pelvic exenteration for neoplasm or post-irradiation necrosis, use of the isolated colon as a conduit obviously simplifies the problem of diversion, and obviates the need for small bowel surgery.

Summary. The search for a substitute for the urinary bladder has centered largely about the use of various portions of the bowel as reservoirs and conduits.

Fifty years' experience has demonstrated the real difficulties of providing a reservoir function, and has defined the factors responsible for dysfunction of such preparations. Obstruction to urine flow, renal infection, and absorption of urinary constituents continue to plague the surgeons and patients associated with such procedures. Their successful management appears to be dependent upon the construction of a satisfactorily functioning ureteral valve.

In the meantime, a conduit made of an isolated segment of bowel, conveying urine quickly to an adherent bag through a cutaneous stoma, appears to offer maximum renal protection and reasonable social convenience.

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OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.
AND
HENRY P. WAGENER, M.D.
ROCHESTER, MINNESOTA

THE OCULAR MANIFESTATIONS OF HYPERCALCEMIA

BY HENRY P. WAGENER, M.D.
EMERITUS MEMBER, SECTION OF OPHTHALMOLOGY, MAYO CLINIC
ROCHESTER, MINNESOTA

IN a number of individuals whose blood calcium is elevated for various reasons, deposits of calcium are visible, especially on slit-lamp examination, in the conjunctiva or the subconjunctival tissues and in the cornea. Reports on the observation of these deposits have appeared in the literature, particularly since attention was focused on them by Walsh and Howard's article published in 1947. Walsh and Howard[37] described the conjunctival deposits as small, glasslike, crystal-clear particles within the ocular conjunctiva in the region of the palpebral fissure. They did not give them any specific name. On the other hand, they classified the corneal deposits as a primary type of band keratitis characterized by hazy, grayish granular epithelial and subepithelial opacities running concentrically with the limbus on the nasal or temporal side or both, densest at the periphery and fading out centrally. They stated that, at times, the opacities involved almost the entire cornea and that they resembled band keratitis ordinarily seen in association with intra-ocular inflammation. They called attention to the presence of clear areas within the opacities which they thought were characteristic of the band keratitis of hypercalcemia. However, Berliner[2] described these clear areas as characteristic of band keratitis due to causes other than hypercalcemia.

Berliner[2] stated that the most common form of band keratitis is characterized by the insidious evolution of a grayish bandlike opacity situated in the exposed interpalpebral zone. The lesions develop first as a turbid area in Bowman's zone at either the temporal or nasal margin of the cornea or both and then spread along a horizontal line to meet centrally and form a band of opacity in which there are scattered dark round fenestrations (holes) of various sizes. The lateral margins of the opacity are separated from the limbus by a clear zone. The older portions of the lesions become white and chalky due probably to hyalinization and calcareous changes which may extend into the subjacent layers of the parenchyma of the cornea. Later, small erosions may develop in the epithelium of the cornea. Berliner described a second and less common type of band keratitis occurring at the limbus which either encircled the cornea or formed an isolated superficial semilunar opaque area in Bowman's zone.

Berliner stated that band-form kera-

titis may develop spontaneously in otherwise unaffected eyes, or secondarily to long-standing intra-ocular inflammation or to exposure of the eye to external irritants. Like Berliner, Doggart[9] included band-shaped opacity among the corneal dystrophies, and he recognized the secondary type, which, he stated, is usually unilateral, and an idiopathic type, which is bilateral. He called attention to the fact that, after calcification develops in the lesion, plaques of calcareous material may work themselves loose and be shed into the conjunctival sac. Neither Berliner[2] nor Doggart[9] mentioned hypercalcemia as a possible cause of band keratitis. But, as noted by Walsh and Howard[37], it is possible that at least some of the conditions diagnosed previously as primary band keratitis were actually caused by hypercalcemia. The term "band keratopathy," suggested by Cogan and his associates[7], is probably a better name for the lesions in the cornea resulting from the deposition of calcium in previously normal corneal tissue as a manifestation of metastatic calcification.

GENERAL CHARACTERISTICS OF THE CORNEAL AND CONJUNCTIVAL LESIONS. Although suggestive individual reports had appeared previously, Walsh and Howard[37] and Cogan, Albright and Bartter[7] were the first to recognize the similarity of the corneal and conjunctival lesions seen in a number of varied disease states and to determine that hypercalcemia was the one factor common to these disease states and, therefore, probably responsible for the ocular lesions.

Walsh and Howard stated that they had first observed the conjunctival deposits 10 years prior to their report and had not seen them in any patient without hypercalcemia. During this 10-year period, they had examined 20 patients with elevated serum calcium and found the typical conjunctival lesions in 8. In 4 of these patients, they found band-shaped opacities in the corneas also. In one additional patient they found opacities in the cornea only. They reported that during a 7-year period band keratitis had been observed in 7 patients with hypercalcemia at the Massachusetts General Hospital, but conjunctival lesions had not been seen. They commented that, as band keratitis of the idiopathic type (without intra-ocular inflammation) is extremely rare, its occurrence in 12 patients with hypercalcemia is striking and probably means that it resulted from the hypercalcemia. In their report published in 1948, Cogan, Albright and Bartter[7] added 12 cases to the 7 previously mentioned by Walsh and Howard as having been observed at the Massachusetts General Hospital. Conjunctival as well as corneal lesions were found in a number of these.

Walsh and Howard[37] seemed to think that the lesions in the conjunctiva were more specific than those in the cornea. However, Cogan and his associates[7] stated that, while the conjunctival opacities might be confused with calcification of the conjunctiva which occurs commonly without definite local or systemic disease, the band opacities in the cornea could be distinguished readily from the white limbal girdle and other opacities which occur "normally." They described the subconjunctival deposits as white flecks or glasslike crystals resembling clusters of fish eggs and the corneal changes as diffuse superficial opacities in the palpebral fissure with a limbal margin that is usually abrupt and concentric with the limbus but separated from it by a clear interval. The axial margin fades away gradually a few millimeters centralward. In a later publication, Walsh and Murray[38] stated that, on slit-lamp examination, the corneal pic-

ture is more specific than the conjunctival, although either may be sufficient to suggest the diagnosis. In the conjunctiva, particularly at the corneal edges, accumulations of elastic tissue (pingueculas), deposits of pigment and fibrous tissue occur frequently and calcification can develop in them as a purely local process. These authors considered an incomplete band characteristic of corneal calcification but described a case of Cogan's in which almost the entire surface of both corneas was calcified. The hypercalcemia in this case was due probably to sarcoidosis.

According to Walsh and Murray[38], the normal concentration of serum calcium is from 9 to 11.5 mg. per 100 ml. and that of serum inorganic phosphorus is from 4.5 to 6 mg. per 100 ml. in children and from 3.3 to 4.0 mg. per 100 ml. in adults. The lowest value for serum calcium recorded in any of the cases reported by Walsh and Howard[38] was 12 mg. per 100 ml. and the highest was 19 mg. per 100 ml. The value for serum calcium in one of the cases reported by Cogan, Albright and Bartter[7] was 8.8 mg. per 100 ml. This case will be discussed later. In all except one of the remaining cases in this series, the level of serum calcium was definitely elevated; in the one exception it was at the upper limit of normal, 11.4 mg. per 100 ml.

Apparently the deposition of calcium in the cornea and conjunctiva can occur rapidly in the presence of a rising concentration of calcium in the blood, and the deposits will regress gradually when the blood calcium returns to normal and remains at normal levels. Walsh and Howard[37] noted the appearance of conjunctival lesions in a patient with post-thyroidectomy hypoparathyroid tetany after administration of calciferol for 15 days. During this time, the concentration of serum calcium rose from 7.7 to 15.8 mg. per 100 ml. The deposits were not present in the conjunctiva on examination 5 months later.

As noted by Walsh and Howard, the symptoms of hypercalcemia *per se* are rather vague and nondescript. Recognition of the distinctive lesions in the cornea and conjunctiva may serve as an important clue to the diagnosis of hypercalcemia when it would not be suspected otherwise. According to Walsh and Murray[38], this metastatic calcification may be an early and even an isolated sign of this disorder. These authors noted that hypercalcemia is present in cases of hyperparathyroidism, vitamin D intoxication, sarcoidosis, multiple myeloma, osteolytic metastatic carcinoma, immobilization because of fractures, excessive intake of milk and alkalis in the treatment of gastrointestinal ulcers, and in beryllium intoxication. Band keratopathy and subconjunctival deposits of calcium have been observed in most of these conditions and also in cases of renal insufficiency due to causes other than excessive intake of milk and alkalis.

SARCOIDOSIS. In 1937, Seefelder[35] reported the occurrence of corneal and conjunctival calcification in cases of Boeck's sarcoid, but, because of the frequency of uveitis in this disease, band keratitis, when present, was regarded usually, as stated by Vogt[36], not as a specific lesion but as a sequel to previous intra-ocular inflammation.

Haldimann[20], however, reported 2 cases in which he considered that hypercalcemia was responsible for the lesions in the cornea and conjunctiva. In the first case, band keratitis and infiltration of the conjunctiva preceded the development of nodular uveitis. The value for blood calcium was 16.3 mg. per 100 ml. and that of inorganic phosphorus 4.3 mg. per 100 ml. In the second case, calcification in the ocular conjunctiva was present at the limbus and in the palpebral fissure areas and

calcification was beginning in the neighboring cornea. The value for blood calcium was 13.6 mg. per 100 ml. and that of the inorganic phosphorus 6.8 mg. per 100 ml.

Cogan, Albright and Bartter[7] included in their series two cases of sarcoidosis, in both of which the concentration of blood calcium was more than 15 mg. per 100 ml. In one of these cases beryllium poisoning was associated. When one of the patients was examined 7 years later, the value for calcium in the blood had fallen to 10 mg. per 100 ml.; the band keratopathy was less marked but there were subepithelial opacities in the conjunctiva. Walsh and Murray[38] mentioned 2 personal cases. Ojers and Alfano[31] found gelatinous nodules and some white flecks in the conjunctiva and a superficial band type of opacity on the nasal and temporal sides of each cornea in a patient with elevated serum calcium in whom the diagnosis of sarcoidosis was established by biopsy of an axillary lymph node. Finely nodular infiltration was observed throughout both lung fields with diffuse and localized calcinosis in both kidneys and multiple deposits of calcium in the soft tissues about the shoulders and hips.

Schüpbach and Wernly[34] added another case in which the band keratitis was associated with iritis in Heerfordt's disease (uveoparotid fever). The value for blood calcium in this case was 16.3 mg. per 100 ml. The authors stated that, in sarcoidosis, it is questionable whether there is pure metastatic calcification (calcium deposition in healthy tissues) or pure dystrophic calcification (calcium deposition in diseased tissues). They were inclined to consider the corneal lesions as metastatic and the conjunctival as dystrophic calcification. They thought that the disturbance of calcium metabolism in sarcoidosis is caused by the bone lesions with perhaps associated chronic renal insufficiency. However, Longcope and Freiman[26] stated that the elevation of blood calcium in cases of sarcoidosis is not definitely related to involvement of bone or to hyperglobulinemia.

Retinopathy was observed in a few cases of sarcoidosis. These will be considered in more detail later with the opthalmologic studies in Goodside's[18] case of primary hyperparathyroidism.

VITAMIN D INTOXICATION. Probably the direct connection between hypercalcemia and deposits of calcium in the cornea and conjunctiva was first recognized in this condition. Meesmann[28] had noted an early band-shaped keratitis in the right eye of a girl with bilateral chronic inflammatory glaucoma. The blood calcium was normal at this time. She was given AT-10 (dihydrotachysterol) for the relief of post-thyroidectomy hypoparathyroid tetany and the concentration of calcium in the blood rose to 14.1 mg. per 100 ml. and remained elevated for about a year in spite of the discontinuance of the AT-10. At the height of the hypercalcemia, extensive calcification of each cornea and some deposits in the neighboring conjunctiva were present. The deposits of calcium diminished gradually so that, when the blood calcium had returned to normal levels, only traces of the deposits were left. This case was reported in 1938, 9 years before the publication of Walsh and Howard's observations[37].

In 1946, Freeman, Rhoads and Yeager[12] described connective tissue and heavy deposits of fat in the conjunctiva of a patient with vitamin D intoxication. In the same year, Paul[32] described in a similar case roughening of the palpebral-fissure portion of the bulbar conjunctiva by numerous little bleblike excrescences, each of which contained an irregular whitish mass which appeared to be calcium. In the

periphery of the cornea, approximately 1 mm. from the limbus, there was a white bandlike infiltrate which was suggestive of beginning zonular dystrophy (band keratitis). Both Paul[32] and Freeman, Rhoads and Yeager[12] suggested that the high intake of milk of their patients enhanced the toxic effect of the vitamin D.

Cases of vitamin D intoxication were included in the series of Walsh and Howard[37], in that of Walsh and Murray[38] and in that of Cogan, Albright and Bartter[7]. These last authors noted that all of their patients with vitamin D poisoning had renal insufficiency. This was true in most of the cases reported by other authors also. Thus 9 of the 10 patients reported by Howard and Meyer[22] had characteristic ocular lesions and all 10 had renal insufficiency. Hyperparathyroidism secondary to the renal lesions may account for the hypercalcemia as suggested by Herbert, Miller and Richardson[21]. However, Howard and Meyer[22] stated that subconjunctival deposits and the lesions of band keratitis might be visible under the slit lamp before renal damage became evident.

Howard and Meyer stated that the lowest dose of vitamin D which produced deposits in the conjunctiva in their cases was 150,000 international units daily for 12 months and that which produced deposits in the cornea was 200,000 units daily for 18 months. Corneal and conjunctival lesions developed in 2 months when the daily dose was 600,000 units.

Deposits in the conjunctiva developed in one patient who received 300,000 units daily for 2 weeks. These authors noted the tendency of the corneal and conjunctival lesions to clear gradually when treatment with vitamin D was discontinued and the patient was given a diet low in calcium. They stated that a rise in the total serum calcium and in its physiologically active components follows administration of large doses of calciferol even if only minimal quantities of calcium are present in the diet, but this effect is enhanced by the administration of calcium salts orally. They suggested that the clearing of the ocular lesions might indicate the possibility of the gradual repair of the damage to the other organs and tissues.

Single cases of vitamin D intoxication with ocular lesions were reported by Gifford and Maguire[16], and by Frost, Sunderman and Leopold[13]. Gifford and Maguire noted clearing of the corneal opacities within 7 months after discontinuing treatment with vitamin D and institution of a diet low in calcium. Frost and associates noted that the toxic symptoms of overdosage of vitamin D might be either acute (nausea, vomiting, abdominal pain and diarrhea) or chronic (related to the presence of metastatic calcification). In their case, they observed in addition to the usual deposits in the cornea and conjunctiva, flesh-colored triangular stony hard plaques on the sclera on either side of the cornea. They pointed out that the corneal lesions must be differentiated from arcus senilis (which starts usually at either the upper or the lower pole of the cornea and is most often located in the deep parenchyma) and from white limbus girdle (which spreads concentrically around the cornea and does not have any interspersed dark areas).

Fleischner and Shalek[10] called attention to the possibility of detecting deposits of calcium in the cornea and conjunctiva by roentgenography. In a case of hypercalcemia induced either by vitamin D intoxication or by immobilization, roentgenograms of the skull disclosed faint calcification in the orbits. This was brought into better relief by use of a "bone-free" technique and dental films. Two types of calcifi-

cation were identified: short rodlike shadows produced by the nodular deposits in, and under the conjunctiva, and linear shell-like shadows corresponding to the calcification in the cornea at the limbus.

Leira[25] reported 4 cases of band keratopathy which he attributed to the hypercalcemia associated with vitamin D intoxication. One of the patients also had sarcoidosis. He stated that the conjunctival changes can regress long before the corneal and long before the blood calcium becomes normal. The corneal changes, on the other hand, can persist long after the serum calcium has returned to normal and after the renal disease, which is present in practically all cases, has been cured. Two of the patients belonged to the same family. This suggested to Leira that a constitutional familial factor of disposition might explain the variable tolerance of individuals to vitamin D.

Ojers and Alfano[31] reported the case of a boy, aged 10 years, with tapetoretinal degeneration and renal rickets, who had been on a regimen of calcium and vitamin D for 5½ months. Gelatinous-appearing nodules with some white flecks were seen in the conjunctiva. The superficial layers of the cornea had an irregular ground-glass appearance, most intense near the limbus. Haziness was noted in the upper and lower portions of the cornea which did not merge with the horizontal cloudy areas. The serum calcium was not definitely elevated, but the authors thought that the combination of irradiated ergosterol and calcium might have caused periodic increases in the serum calcium which would account for the deposition of calcium in the cornea and conjunctiva.

Ojers and Alfano[31] stated that, in renal rickets, the renal tubules are so damaged that they are no longer able to manufacture sufficient base (ammonium) with which to excrete acids. Calcium may be utilized as a substitute for the ammonium radical. Thus the concentration of serum calcium tends to decrease and parathyroid hyperplasia results. However, because of the glomerular damage, the parathyroid hormones cannot induce diuresis of phosphorus and hence calcium is deposited in the osteoid tissues. It should be recalled that, in some cases of renal rickets, cystine crystals are deposited in the cornea and conjunctiva. These crystals were described by Goar and de la Motte[17] as tiny white dots studding the entire superficial layers of the cornea which are seen to be iridescent crystals under higher magnification.

IMMOBILIZATION. It is of interest that Walsh and Murray[38] reported a case of ocular calcification due to hypercalcemia resulting from immobilization.

PRIMARY HYPERPARATHYROIDISM. Cases of primary hyperparathyroidism were included in the series reported by Walsh and Howard[37] and by Walsh and Murray[38]. The latter stated that metastatic calcification in the ocular tissues occurs in a minority of cases of primary adenoma of the parathyroid. Calcification of the cornea or conjunctiva or both was found in 5 of the 16 patients examined with the slit lamp. Cogan, Albright and Bartter[7] found calcification in the cornea or conjunctiva or both in 3 cases of parathyroid adenoma and in one case of carcinoma of the parathyroid. All of their patients had either nephrocalcinosis or nephrolithiasis. Aside from these observations, reports of corneal or conjunctival involvement in primary hyperparathyroidism are rather scanty. Galindez-Iglesias and Lafuente[14] described bilateral conjunctival nodules in a case of hyperparathyroidism with hypercalcemia. Folk's case[11] will be dis-

cussed in the section on the milk-alkali syndrome. Goodside[18] observed in a woman, aged 25 years, who had 17.7 mg. of calcium and 2.9 mg. of inorganic phosphorus per 100 ml. of serum, chalk-white lines in the cornea of each eye extending about 4 mm. along the limbus at the temporal and nasal sides. Central to these calcium lines and separated from them by a clear interval was a fainter superficial opacity in the cornea. Necropsy revealed an adenoma of the right inferior parathyroid with hyperparathyroidism, extensive skeletal demineralization and generalized calcinosis.

Ophthalmoscopic examination of Goodside's[18] patient revealed that the disks were pale, the retinal vessels attenuated and that "scattered throughout the central areas were very numerous pale-pink, poorly defined lesions of many shapes lying underneath the retinal vessels. In many areas they were coalescent and in the macula they became larger, reaching the size of 0.25 disc diameter. Between these patches there appeared an increase in retinal pigmentation in many areas. Inferior to the left disc the retina seemed edematous. The nature of the patches was uncertain."

Walsh and Murray[38] found retinopathy in only one of their cases of hypercalcemia. This patient had moderate hypertension and an unusually severe choroidal sclerosis. Sarcoidosis was a possible but not proved cause of the hypercalcemia. Haldimann[20] found several scattered whitish and yellow spots in the fundi of one of his patients with sarcoidosis. Klinefelter and Salley[24] observed a retinopathy resembling that seen in association with multiple myeloma in a patient with sarcoidosis which simulated glomerulonephritis. The retinopathy in this case was due probably to the hyperproteinemia and the hyperglobulinemia which were present. The value for serum calcium was 17.7 mg. per 100 ml.; but the authors did not mention the presence of metastatic calcification.

HYPERCALCEMIA ASSOCIATED WITH EXCESSIVE INTAKE OF MILK AND ALKALI. In 1949, Burnett, Cummons, Albright and Howard[5] reported 6 cases of a syndrome characterized by a history of prolonged and excessive intake of milk and absorbable alkali, hypercalcemia without hypercalciuria or hypophosphatemia, normal level of serum alkaline phosphatase, marked renal insufficiency with azotemia, mild alkalosis, calcinosis manifested especially by an ocular lesion resembling band keratitis, and an improvement in the clinical state on an intake low in milk and absorbable alkali. All of these cases had been included previously in the reports of Walsh and Howard[37] or of Cogan, Albright and Bartter[7]. All of the patients had band keratopathy and 2 of them had also small glasslike particles in the conjunctiva. Metastatic calcification was present in other tissues also in 5 of the patients. This was irregular in distribution and varied from widespread soft-tissue calcification to calcification of a few mesenteric nodes. The authors thought that the hypercalcemia was secondary to renal damage and resultant fixation of urinary excretion of calcium. Walsh and Murray[38] included only one case in which alkali had been used in treatment of peptic ulcer in their group of cases of hypercalcemia and raised the question of possible parathyroid tumor in this case.

In this connection it is of interest that Folk[11] reported the case of a man, aged 51 years, with a history of recurrent symptoms of ulcer and excessive intake of alkali for 25 years. He was oliguric and azotemic. Fine, white, subepithelial deposits were present in each cornea adjacent to

the limbus; these extended 2 to 3 mm. into the cornea and were confined principally to the interpalpebral zone. Intra-ocular tension was normal. Five years later the calcification had extended 3 to 3.5 mm. into the cornea, and roentgenograms of the globes revealed diffuse calcification. Chronic simple glaucoma had developed in each eye. The patient died as a result of myocardial infarction. Necropsy revealed multiple cardiac infarcts, bilateral polycystic kidneys, chronic stomal ulcer and a parathyroid adenoma. There was metastatic calcification of the dura, blood vessels, kidney, trachea and joint capsules. The level of serum calcium of this patient ranged between 9.7 and 11.6 mg. per 100 ml. and that of the serum inorganic phosphorus between 2.0 and 5.8 mg. per 100 ml.

Folk[11] thought that the primary functioning parathyroid adenoma had caused nephrocalcinosis. The chronic hypochloremic alkalosis resulting from the kidney damage was intensified by chronic vomiting and the high intake of alkali. The chronic alkalosis plus a functioning parathyroid adenoma in the presence of a normal serum calcium and slightly elevated inorganic phosphorus resulted in the diffuse calcification, in which the cornea and sclera participated, because of the tendency toward precipitation of calcium salts in an alkaline medium.

In the case reported by Wermer, Kuschner and Riley[39], ingestion of milk and absorbable alkalis was discontinued and after 6 months the glasslike deposits in the conjunctiva had disappeared but the band keratitis was still present. In the case reported by Miller, Freeman and Heath[29], the serum calcium returned to normal levels and the renal function improved but the calcium deposits in the eyes and in the lumbar region did not change. McQueen[27] observed white chalklike plaques in the sclera of each eye of a patient with duodenal ulcer who was drinking a gallon of milk a day and was taking alkaline powders. Scholz and Keating[33] reviewed 8 cases of the milk-alkali syndrome with renal insufficiency and hypercalcemia; deposits of calcium in the cornea were found in only one of the 8 cases.

HYPERCALCEMIA IN RENAL INSUFFICIENCY. Cogan, Albright and Bartter found deposits of calcium in the cornea and conjunctiva of 8 uremic patients. Five of these patients were consuming large amounts of milk and alkalis. Two gave a history of prolonged vomiting of undetermined cause and nephrocalcinosis may have developed secondary to the chronic alkalosis resulting from the vomiting. In one of these 2 patients, biopsy of 2 parathyroid glands showed secondary hyperplasia. In the eighth patient, roentgenograms showed skeletal decalcification with bone cysts, osteoarthritis, a calcified deposit near the right elbow and contracted kidneys; a definite diagnosis was not established. In a patient presumed to have hyperparathyroidism secondary to renal disease, Ojers and Alfano[31] observed in the conjunctiva of each eye, immediately adjacent to the corneal limbus on both nasal and temporal sides, clear yellowish nodules, some with white flecks at their apex. Roentgenograms showed cystic changes in the ribs and in the right clavicle and demineralization of the skull, pelvis, humerus and femur. The value for serum calcium was 10.6 mg. per 100 ml. at the time of examination of the eyes but was said to have been elevated previously.

CHEMICAL AND HISTOLOGIC EXAMINATIONS OF THE OCULAR TISSUES IN CASES OF HYPERCALCEMIA. Chemical examination of a specimen obtained by biopsy from the conjunctiva of one of Walsh and Howard's[37] cases of hyperpara-

thyroidism showed that the material deposited was probably calcium phosphate. Galindez-Iglesias and Lafuente[14] stated that chemical analysis of a conjunctival nodule from their case of hyperparathyroidism showed that it consisted of tricalcium phosphate.

Microscopic examination of a specimen obtained for biopsy from the conjunctiva of one of Walsh and Howard's cases of vitamin D intoxication showed an amorphous material more refractile than the rest of the tissue just beneath the basal layer in the most superficial connective tissue. Von Kossa stain showed that this material contained calcium.

The right eye of one of Cogan, Albright and Bartter's[7] patients with the milk-alkali syndrome had been removed because of painful glaucoma 3 years prior to their examination. At the time of removal, practically the entire cornea of the right eye was infiltrated with calcium and there were opacities on the nasal and temporal margins of the left cornea. Histologic examination of the right cornea showed that the posterior surface and the stroma were not abnormal. Bowman's membrane was intact and appeared normal in its axial portion but became increasingly calcified toward the periphery. The calcification was densest at the limbal extremity of Bowman's membrane, and spread into the superficial stroma. Anterior to Bowman's membrane was a newly-formed connective tissue membrane. In the anterior part of this membrane were calcific plaques some of which were erupting through to the surface of the cornea. Areas of calcification were present also in the superficial layers of the sclera over the ciliary body. The authors thought that the clear lacunae seen clinically within the areas of corneal opacity in cases with calcification of the cornea result probably from the sloughing of calcific plaques which have erupted through to the surface as demonstrated in the sections of this case.

In one of Haldimann's[20] cases of sarcoidosis, biopsy of the conjunctiva resulted in a diagnosis of tuberculosis; but a second biopsy, 2 years later, showed only massive calcification and foreign-body, giant-cell reaction. Biopsy of the conjunctiva in Haldimann's second case showed subepithelial calcification and hyaline degeneration. Frost, Sunderman and Leopold[13] stated that scrapings from the flesh-colored lesions in the deep bulbar conjunctiva and sclera in their case of vitamin D intoxication indicated the presence of calcium. Histologic examination of the eye obtained at necropsy from Goodside's[18] case of parathyroid adenoma showed plaques of calcium and bone in the sclera in the ciliary region, in the region of the ora serrata and posterior to the equator. One plaque involved the suprachoroid. There was a mild chronic inflammatory reaction in the uveal tissue. Amorphous deposits of calcium were noted in the subconjunctiva at the limbus. One deposit formed a straight line which was continuous with Bowman's membrane. The membrane itself was calcified for a short distance from the limbus, the calcification becoming increasingly less definite axialward. Goodside[18] thought that the pale-pink areas observed ophthalmoscopically in the fundi were related to the calcium plaques in the sclera either through transmitted pressure or through a local inflammatory response in the choroid.

The histopathologic diagnoses of the ocular lesions in Folk's case[11] of parathyroid adenoma with excessive intake of alkali were glaucoma, band-form keratitis, calcified plaques in the sclera, scleritis, chronic choroiditis, uveal and retinal vascular sclerosis, ganglioform degeneration (inspissated exudates)

and gliosis of the retina and optic atrophy. In the cornea, Bowman's membrane was intact but ribbonlike areas of hyalinization were present, especially in its peripheral portions. Scattered areas of early hyaline necrosis and dystrophic changes were found in the stroma. Large hyalinized plaques were present in the sclera, mainly in the posterior portion; some of these had undergone calcification. Interspersed among these plaques were round cells, plasma cells and macrophages. In their description of Cogan's case of probable sarcoidosis with diffuse superficial opacification of almost the whole of each cornea, Walsh and Murray[38] stated, "bone-free X-ray films of the eyes failed to show calcium, but, with von Kossa stain, it was shown that there was calcium present beneath the epithelium of one cornea so tested."

Gartner and Rubner[15] reported 2 cases of calcification of the ocular tissues associated with hypercalcemia resulting from vitamin D intoxication. In one of their cases, the eye was not seen clinically but at necropsy showed histologically calcification in healing scleral nodules and also calcified plaques in the subconjunctival tissues at the limbus. Band-formed keratitis and yellowish patches on the sclera were observed clinically in their second case. Roentgenologic examination with bone-free technique showed that these patches had the density of calcium.

MECHANISM OF METASTATIC CALCIFICATION IN THE OCULAR TISSUES IN HYPERCALCEMIA. Walsh and Howard[37] stated that pathologic calcification is of two types: in the first, a local process, usually degenerative, has produced conditions conducive to the deposition of lime salts; in the second, a systemic diseased state is present which is accompanied by changes in the concentration of ionized calcium or inorganic phosphorus or both in the serum. The ocular lesions in cases of hypercalcemia are of the second type, but some factor other than hypercalcemia must be concerned in their production, for they are not seen in all cases of vitamin D poisoning or of hyperparathyroidism and there is no apparent correlation between their appearance and the degree of elevation of the serum calcium or the duration of the disease state.

Bauer and Freyberg[1] stated that, in vitamin D intoxication with metastatic calcification, some authors think that cellular damage comes first and that calcium is deposited then in the injured areas. Others think that the pathologic calcification is not preceded by cellular damage. Danowski, Winkler and Peters[5] said that vitamin D in large doses provokes hypercalcemia and increases the calcium content of the soft tissues, particularly of the kidneys. The hypercalcemia favors metastatic calcification. This may be facilitated by local tissue injury, already present or produced by the vitamin D itself. In discussing the corneal calcification which had developed in a patient within 6 to 8 weeks of the beginning of vitamin D administration, Cogan[6] gave his explanation of the local mechanism of corneal calcification. Extravascular fluid diffuses into the cornea from the periphery, and water is selectively abstracted from this fluid through the semi-permeable membrane at the surface of the cornea. This results locally in a concentration of electrolytes beneath the surface membranes and those electrolytes which are near saturation level to begin with will precipitate out. Thus the formation of the calcific deposit beneath the epithelium is a supersaturation and not a necrobiotic process. The loss of carbon dioxide through the epithelium may also be of significance in localizing the deposition of calcium. The location of the deposits mainly in the palpebral-fissure areas of

the cornea and conjunctiva may be explained, as suggested by Haldimann[20], by the fact that the loss of fluid through contact with air favors the deposition of calcium.

In discussing the corneal and conjunctival lesions seen in cases of milk-alkali syndrome, Cogan, Albright and Bartter[7] stated that renal damage (nephrocalcinosis?) is believed to result from high intake of calcium and alkali. The pathogenesis of the band keratopathy would presumably be the same as that of the calcification of the kidneys. This may not be true necessarily in all cases of hypercalcemia. Jeans[23] said that toxic doses of vitamin D remove calcium and its associated minerals from the stores in bones and increase the calcium level in plasma. Increased excretion of calcium in the urine may cause deposits of calcium in the kidneys with decreased renal function. According to Freeman, Rhoads and Yeager[12], numerous studies have demonstrated that the absolute as well as the relative amounts of calcium and phosphorus in the diet influence the toxicity of vitamin D, and that studies of calcium balance on a patient who was receiving Ertron (activated ergosterol) and a high-calcium diet indicated that increased urinary excretion of calcium and conditions favorable to the deposition of calcium in the kidney may precede, and need not be accompanied by, hypercalcemia.

With reference to one of their patients with uremia and deposits of calcium in the cornea and conjunctiva who had 8.8 mg. of calcium per 100 ml. and 8.9 to 10.1 mg. of inorganic phosphorus per 100 ml. of serum, Cogan, Albright and Bartter[7] commented, "We are not prepared to state to what extent band keratopathy may occur with renal damage and rising serum inorganic phosphorus in cases in which there is not a pre-existing hypercalcemia. Whereas the data on Case 16 suggest that this change in the cornea may occur, the patient was first seen in the terminal stage of her disease, at a time when the serum nonprotein nitrogen and inorganic phosphorus levels were very high. The normal serum calcium may or may not have been preceded by a high level." With reference to this question, Jeans[23] stated that metastatic calcification is associated usually with hypercalcemia and hyperphosphatemia but can occur without an increase in the level of calcium in the blood. And Bauer and Freyberg[1] made the statement that, in experimental animals, pathologic calcification may occur without hypercalcemia and seemed to depend more on fluctuations of serum calcium than on hypercalcemia *per se*.

The general opinion seems to be that combined hypercalcemia and hyperphosphatemia is necessary for the production of metastatic calcification. Thus Wermer, Kuschner and Riley[39] stated that "as already indicated, oversaturation of the serum with calcium and phosphorus is the chief prerequisite for the occurrence of metastatic calcification." Mulligan[30] said, with reference to the metastatic calcification associated with vitamin D intoxication and high intake of alkalis, that the reasons for the extensive direct calcification of soft tissues probably include hypercalcemia, retention of phosphates, mobilization of calcium phosphate from the bones, a high alkaline diet, an excess of ingested phosphate, and the enhancement of calcium retention by the intake of sodium bicarbonate. Herbert, Miller and Richardson[21] commented that, if the view is accepted that the concentrations of calcium and phosphate in normal plasma fall near to the saturation level for calcium phosphate, then, if one of these ions rises above normal without a corresponding fall in the other, the saturation level is likely to be exceeded

and the deposition of calcium phosphate in the soft tissues is just what would be expected.

Wermer, Kuschner and Riley[39] stated that metastatic calcification may be subdivided into cases with hyperparathyroidism which may be either primary or secondary to chronic renal disease and long-standing renal insufficiency and cases with normal parathyroid function. According to these authors, "Hypercalcemia *per se* does not ordinarily suffice to cause metastatic calcification. The reported cases of primary hyperparathyroidism, with metastatic calcification, invariably have been in severe renal failure with hyperphosphatemia for a prolonged period." However, this seems not to have been true in the 4 cases of hyperparathyroidism with band keratopathy or conjunctival deposits or both reported by Cogan, Albright and Bartter[7], or in the case reported by Goodside[18]. The serum inorganic phosphorus was not elevated in any of these cases, the highest level being 3.7 mg. per 100 ml. Wermer, Kuschner and Riley[39] said further that metastatic calcification in the presence of normal parathyroid function can occur only if there is an oversupply of calcium and phosphorus that reaches the blood from endogenous or exogenous sources. As has been stated previously, there seem to be certain exceptions to this rule also. So it cannot be assumed that the problem of the mechanism of metastatic calcification has been entirely resolved.

TREATMENT OF CORNEAL CALCIFICATION IN CASES OF HYPERCALCEMIA. As the corneal opacification which occurs in cases of hypercalcemia is seldom sufficient to interfere with vision and as there is a tendency to reversal of the opacities when measures for the reduction of the hypercalcemia are instituted, local treatment of the cornea is not often necessary. However, if the opacities are situated axially so that they interfere with vision or if the calcific deposits are being extruded spontaneously through the corneal epithelium and causing irritation of the eyes, they can be successfully removed, according to Grant[19], by treatment with a solution of the neutral sodium salt of ethylenediamine tetraacetic acid. Breinin and DeVoe[4] expressed the opinion that calcium chelation should be the primary treatment for band keratopathy, for irritating calcareous infiltration of the cornea and for the early treatment of lime burns of the cornea and conjunctiva. They stated originally that the chelating drug used was edathamil calcium-disodium. But Breinin[3] corrected this later and said that the drug used was really the disodium salt of ethylenediamine tetraacetic acid adjusted (to neutrality) with sodium bicarbonate.

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PHYSIOLOGY

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF OCTOBER 18, 1955

INFORMAL SEMINAR OF MECHANISMS OF GASTROINTESTINAL SECRETION

Introductory Remarks on the Symposium on Gastrointestinal Secretion. M. H. F. FRIEDMAN, PH.D., (Department of Physiology, Jefferson Medical College). The major problems facing the gastrointestinal physiologist are those concerned with mechanisms of secretion and transport. New techniques including ultracentrifugation, electrophoresis, paper chromatography and electron microscopy (to mention only a few) have opened new directions of attack. Dr. Hogben has evidence that in H ion transport during the formation of hydrochloric acid there is also an active transport of both Cl ion and water: this is in contrast to theories that only H ion transport is active, while transfers of Cl and water are passive. This should suggest new points of concentration in attempts to reduce acid secretion. The findings of Dr. Komarov are of great significance. He concludes that all proteins of the gastric juice are mucoproteins and implies that the chief cell (pepsin) and the mucoid cell (mucus) are interrelated. Taken to its ultimate conclusion, this would suggest that basically the gastric glands and epithelium consist of only two kinds of cells: one for acid secretion and the other for protein secretion. Dr. Thomas points out that the bicarbonate of pancreatic secretion is derived from both the blood and the organ's own metabolic activity: his suggestion that the gastric acid-secreting cell and the pancreatic bicarbonate-secreting cell are essentially mirror images of each other offers an excellent working hypothesis to bring a common denominator to ion transport mechanisms. Although it is usually believed that bicarbonate and enzyme secretions emanate from the same cell, Dr. Thomas' suggestion that the bicarbonate comes from the intralobular cell offers an explanation for the finding of a partition in the enzyme and bicarbonate secretions in chronic pancreatitis.

The Formation of Gastric Acid. C. ADRIAN M. HOGBEN, M.D. (National Heart Institute, Bethesda, Maryland.) The gastric mucosa actively transports Cl^- and transports Cl^- at a faster rate than H^+. The resultant excess of negative ions can be quantitatively idenfied as the mucosal short-circuit current. The ratio of Cl^- to H^+ transported by short-circuited mucosa is greater than 3, suggesting that the respiratory efficiency of Cl^- transport is greater than 4. Gastric epithelial cells have a high Cl^- content, about 2/3 that of the bathing solutions. An apparent slow exchange of intracellular Cl^- can be attributed to the much greater turnover of Cl^- across the lumenal surface of these cells. SCN^-, like Cl^-, is also transported but more slowly and is more dependent on the electrical potential. Competition kinetics indicate that a single carrier reaction will prove insufficient to analyse anion transport.

Carbonic anhydrase plays an important but not an obligatory role. At the low rate of H^+ secretion of the isolated frog mucosa, acetazolamide inhibits H^+ secretion by 40%. The spontaneous potential and short-circuit cur-

rent are reversibly depressed by 75%. This carbonic anhydrase inhibitor inhibits both Cl^- and H^+ transport and under the conditions of these experiments the former effect predominates.

It has been a working assumption that water movement in gastric secretion is passive, secondary to solute movement. Frank *et al.* (J. Gen. Physiol., in press) observed spontaneous secretion of 15 microl. $cm.^{-2}$ $hr.^{-1}$ which was increased twofold by a 100 mOsM. gradient. With any reasonable geometric model for the epithelium, it would be necessary to postulate that a negligible osmotic gradient is effective for spontaneous secretion, while a striking imposed osmotic gradient only results in a limited increase.

Formation of Pepsin and Mucus. S. A. Komarov, M.D., Ph.D. (Fels Research Institute, Temple University School of Medicine.) Fractionation of gastric juice revealed the presence of several proteins in canine and human secretions (Review in J. Natl. Cancer Inst., 13, 1007, 1953). Of these only pepsin was isolated in relatively pure state from uncontaminated canine gastric juice (Shumov-Simanovski, 1894; Pekelharing, 1902), and was shown to possess some characteristics of globulins; and most likely is secreted by the peptic cells. Presence of two different kinds of mucoproteins has been demonstrated in gastric mucus and in acid gastric juice. One of them was shown to have mucoitin sulfuric acid as a prosthetic group, and is probably secreted by mucoid cells of the neck of the glands. The other mucoprotein, on circumstantial evidence, may be regarded as having "neutral polysaccharide" as a prosthetic group and is apparently secreted by the surface epithelium cells. These mucoproteins were found in varying proportions and concentrations in viscous mucus and also in acid gastric juice secreted in response to shamfeeding or histamine. A fourth well-defined but unnamed and not sufficiently studied protein was reported as a normal constituent of gastric juice present only in exceedingly small amounts. Other proteins, reported as components of gastric juice were not sufficiently studied to permit definite conclusions. Electrophoresis of canine gastric juice at pH 6.0 corroborated evidence obtained by other methods and demonstrated at least four acidic protein fractions and one very small basic fraction. All acidic fractions had a rather low nitrogen content, contained uronic acid and, in larger molecular concentrations, hexosamine. These acidic fractions all possessed peptic power but with varying specific activity, which in some was equal to that of crystalline pepsin. No fraction with mobilities similar to that of crystalline pepsin was observed in the patterns so far obtained. Added crystalline pepsin was separated as a peak with higher mobilities than any obtained in the gastric juice itself. A general conclusion seems to be justified in that all proteins of gastric juice are mucoproteins.

The secretion of all protein components is stimulated, in varying degrees by the parasympathetic or "cephalic" mechanism but not by histamine. Local physical and chemical stimuli, sodium dodecyl sulfate among them, are effective stimuli for a viscous mucus particularly rich in derivatives of "neutral polysaccharide."

Formation of Bicarbonate by the Pancreas. J. E. Thomas, M.D. (Department of Physiology, Jefferson Medical College.) The following problems were discussed: Conditions determining the concentration of bicarbonate in pancreatic juice; the source of the bicarbonate; the type of pancreatic cell producing bicarbonate; and the mechanism of bicarbonate secretion.

It was pointed out that bicarbonate concentration is related to the rate of secretion, the relationship being: log bicarbonate (mE/L) = a + b $\frac{1}{\text{rate}}$, a and b having their usual significance in the equation of a linear graph and rate expressed as ml./min./kg.

The source of the bicarbonate is still undetermined but apparently some comes from the blood and some from the metabolic CO_2 of the pancreas. The best available evidence indicates that no more than 20% comes from the metabolic CO_2.

It was suggested that the intralobular duct cells may secrete bicarbonate. The older idea that bicarbonate is secreted by the acinar cells presents certain theoretical difficulties. The mechanism of secretion of bicarbonate is unknown and little or no work is being done on the problem. It was pointed out that the gastric glands also secrete bicarbonate, presumably into the blood, and that the mechanism for secretion may be the same in the pancreas.

The work of the following (senior) authors was cited: S. S. Conly, 1955; B. Goldstein, 1931; E. Hammarsten, 1928; H. F. Tucker, 1941; E. G. Ball, 1930, 1941; W. M. Hart, 1945; E. W. Still, 1933; M. H. F. Friedman, 1947; H. Lagerlöf, 1939; D. Birnbaum, 1953; D. A. Dreiling, 1955; E. L. Montgomery, 1941; and others.

BOOK REVIEWS AND NOTICES

LETALFAKTOREN IN IHRER BEDEUTUNG FÜR ERBPATHOLOGIE UND GENPHYSIOLOGIE DER ENTWICKLUNG. By PROF. ERNST HADORN, Professor of Zoology, University of Zurich. Pp. 338; 129 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $9.30.

THIS is a scholarly presentation of what is known on the subject of lethal factors with the purpose of establishing a general and special heredopathology of development. The author, a Professor of Zoology and Comparative Anatomy, has drawn his material largely from the field of animal genetics, but there are a number of references to both human and plant genetics. Those interested in this field will find here an extremely valuable contribution. The numerous illustrations are excellent and there is an adequate bibliography. The style is simple and clear so that those with a reasonable command of German will have no difficulty. The excellence of this work would justify its translation into other languages. R. K.

COUGH SYNCOPE. By VINCENT J. DERBES, M.D., Professor of Medicine, Tulane University School of Medicine, AND ANDREW KERR, JR., M.D., Assistant Professor of Medicine, Louisiana State University School of Medicine. Pp. 182; 8 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.75.

THIS is a well written monograph on a condition that is by no means rare and that is potentially dangerous. The book presents a detailed clinical picture of cough syncope and numerous illustrative case reports with discussions of theories of mechanism. There are also discussed related conditions with which the disease might be confused: syncope, narcolepsy-cataplexy, epilepsy, the laryngeal crises of tabes, and voluntary death by breath holding. The book is well recommended. R. K.

THE MASK OF SANITY. By HERVEY CLECKLEY, M.D. Pp. 596. St. Louis: C. V. Mosby Co., 1955. Price, $9.50.

THIS book, according to the author, sets out "to clarify some issues about the so-called psychopathic personality." Some good case histories are given. A clearer recognition of the various facets of this type of mental disorder can be obtained from reading this volume. The author admits that treatment is difficult and to date disappointing but says, "If medicolegal agreement could be reached and our present hospitals given the ability to hold and deal sensibly with incompetent patients of this sort as they now can with others who are incompetent, a primary and major step would be achieved. Better results might be obtained if effective control of the situation could be maintained in institutions and through well-supervised systems of parole and gradual rehabilitation in those qualifying for outpatient status."

There is a long list of references and an index. O. E.

BICKHAM-CALLANDER SURGERY OF THE ALIMENTARY TRACT, VOLS. I, II AND III. By RICHARD T. SHACKELFORD, M.D., Assistant Professor of Surgery, Johns Hopkins University School of Medicine, and HAMMOND J. DUGAN, M.D., Assistant in Surgery, Johns Hopkins University School of Medicine. Pp. 2575; 1705 ills. Philadelphia: W. B. Saunders Company, 1955. Price, $60 the set.

ABOUT six years ago, Dr. Richart T. Shackelford undertook the prodigious task of revising Bickham-Callander's monumental work, "Surgery of the Alimentary Tract." Doctor Shackelford began this revision in 1949, believing that he could do the job in approximately a year. Six years later, the job was completed and the reviewer considers the time well spent. The extensive bibliography at the end of each chapter is an indication of the completeness with which the subject has been covered.

The three volumes are said to be a second edition of Bickham's Operative Surgery. It is really a new authoritative work on surgery of the alimentary tract. It combines and simplifies the best work and thoughts of recent and current surgical authorities. Many of the excellent illustrations are taken from the best writings of America's foremost surgeons. It seems proper to mention the specific subjects covered. The first volume discusses the esophagus, stomach and duodenum, liver, gallbladder and extrahepatic biliary ducts. The second volume covers the pancreas, spleen, small intestine, peritoneum, omenta, mesentery and colon. The third volume co-

ers the anorectal tract, excisions of the rectum, herniae of the gastrointestinal tract and incisions in general.

It is, of course, impossible for any one work to cover completely such a varied subject, but Doctor Shackelford's effort is a most worthy one. Not only is surgical technique discussed thoroughly, but the basic physiology-pathology is so clearly explained that I hardly see how any general surgeon, from resident to professor, can fail to be fascinated by it. G. R.

Psychische Hygiene. Edited by Ernst Brezina and Erwin Stransky. Pp. 282. Vienna: Wilhelm Maudrich, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $8.25.

This book is an introduction into the vast field of mental hygiene. After a historical chapter (W. Holzer), there are chapters on the development of the field of mental hygiene (W. Beers), on the relationship of mental hygiene to clinical psychiatry (E. Stransky), to psychotherapy (H. Kogerer), to somatic hygiene (E. Brezina), to child psychiatry (H. Asperger), to geriatrics (E. Stransky), to sexual and mental problems (F. Stengel, A. Niedermeyer), to suicide (Menninger, Lerchenthal), to industrial problems (R. Jech), to criminologic problems (E. Stransky), to sociologic problems (Kogerer, Smekal-Huber) and to alcoholism (Kogerer). This text will probably serve well its purpose to introduce Austrian practitioners and social workers to these important problems.

E. S.

The Story of Medicine. By Kenneth Walker, M.A., M.B., F.R.C.S. Pp. 343; 51 ills. New York: Oxford University Press, 1955. Price, $6.00.

The author's purpose in writing this book appears to have been to produce something readable and attractive for lay consumption. In this he has fully succeeded. At the same time he has managed to give an adequate coverage of essentials. In the first part of the book the important medical discoveries are discussed in a fairly chronological order. Later sections are devoted to practical medical problems and so have a less personal aspect. There is some tendency, in the interest of readability, to overemphasize items that might catch the layman's interest and to gloss over important but less attractive items. A section on "Deficiency Diseases" includes not only the avitaminoses but all that the book contains about the endocrine organs. The name "Wassermann" is mispelled both in the text and the index. In speaking of the vicissitudes attending the introduction of vaccination against smallpox, the author refers to an American who recently inspired a three-volume biography as " a certain Mr. Cotton Mather." However, these are minor items. The layman will find the book instructive as well as very readable. R. K.

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M.D., Consultant in Medicine, Massachusetts General Hospital. American Lecture Series No. 242. Pp. 186; 35 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $5.50.

This little book contains much practical advice, not only for the general practitioner but also for the internist and the medical student, as an aid to the diagnosis and treatment of heart disease. It could have been written only by a past master in the field.

R. K.

Gestation. Transactions of the First Conference, March 9, 10, and 11, 1954, Princeton N. J. Edited by Louis B. Flexner, M.D., Professor and Chairman, Department of Anatomy, University of Pennsylvania School of Medicine. Pp. 238; 97 ills. including 4 color plates. New York: Josiah Macy, Jr. Foundation, 1955. Price, $5.00.

The first conference on Gestation which was sponsored by the Josiah Macy, Jr. Foundation and reported in this volume was limited to the structure and function of the placenta. The members of the conference were anatomists, physiologists, biologists, chemists, embryologists and obstetricians, each of whom had a particular interest and considerable experience with some specific phase of placental structure or function. This represents, therefore, the most authoritative current information on the placenta.

The material is presented informally as it was discussed in the conferences and though definite topics were assigned to specific individuals for presentation little of the text is comparable to the orderly presentation of material in the usual scientific paper. Rather, it consists of statements, challenges, explanations, arguments and presentation of work in progress or completed experiments concerning "The Functional Role of the Placenta," "Problems of Sugar Transport in the Placenta of

BOOK REVIEWS AND NOTICES

LETALFAKTOREN IN IHRER BEDEUTUNG FÜR ERBPATHOLOGIE UND GENPHYSIOLOGIE DER ENTWICKLUNG. By PROF. ERNST HADORN, Professor of Zoology, University of Zurich. Pp. 338; 129 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $9.30.

THIS is a scholarly presentation of what is known on the subject of lethal factors with the purpose of establishing a general and special heredopathology of development. The author, a Professor of Zoology and Comparative Anatomy, has drawn his material largely from the field of animal genetics, but there are a number of references to both human and plant genetics. Those interested in this field will find here an extremely valuable contribution. The numerous illustrations are excellent and there is an adequate bibliography. The style is simple and clear so that those with a reasonable command of German will have no difficulty. The excellence of this work would justify its translation into other languages. R. K.

COUGH SYNCOPE. By VINCENT J. DERBES, M.D., Professor of Medicine, Tulane University School of Medicine, AND ANDREW KERR, JR., M.D., Assistant Professor of Medicine, Louisiana State University School of Medicine. Pp. 182; 8 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $4.75.

THIS is a well written monograph on a condition that is by no means rare and that is potentially dangerous. The book presents a detailed clinical picture of cough syncope and numerous illustrative case reports with discussions of theories of mechanism. There are also discussed related conditions with which the disease might be confused: syncope, narcolepsy-cataplexy, epilepsy, the laryngeal crises of tabes, and voluntary death by breath holding. The book is well recommended. R. K.

THE MASK OF SANITY. By HERVEY CLECKLEY, M.D. Pp. 596. St. Louis: C. V. Mosby Co., 1955. Price, $9.50.

THIS book, according to the author, sets out "to clarify some issues about the so-called psychopathic personality." Some good case histories are given. A clearer recognition of the various facets of this type of mental disorder can be obtained from reading this volume. The author admits that treatment is difficult and to date disappointing but says, "If medicolegal agreement could be reached and our present hospitals given the ability to hold and deal sensibly with incompetent patients of this sort as they now can with others who are incompetent, a primary and major step would be achieved. Better results might be obtained if effective control of the situation could be maintained in institutions and through well-supervised systems of parole and gradual rehabilitation in those qualifying for outpatient status."

There is a long list of references and an index. O. E.

BICKHAM-CALLANDER SURGERY OF THE ALIMENTARY TRACT, VOLS. I, II AND III. By RICHARD T. SHACKELFORD, M.D., Assistant Professor of Surgery, Johns Hopkins University School of Medicine, and HAMMOND J. DUGAN, M.D., Assistant in Surgery, Johns Hopkins University School of Medicine. Pp. 2575; 1705 ills. Philadelphia: W. B. Saunders Company, 1955. Price, $60 the set.

ABOUT six years ago, Dr. Richart T. Shackelford undertook the prodigious task of revising Bickham-Callander's monumental work, "Surgery of the Alimentary Tract." Doctor Shackelford began this revision in 1949, believing that he could do the job in approximately a year. Six years later, the job was completed and the reviewer considers the time well spent. The extensive bibliography at the end of each chapter is an indication of the completeness with which the subject has been covered.

The three volumes are said to be a second edition of Bickham's Operative Surgery. It is really a new authoritative work on surgery of the alimentary tract. It combines and simplifies the best work and thoughts of recent and current surgical authorities. Many of the excellent illustrations are taken from the best writings of America's foremost surgeons. It seems proper to mention the specific subjects covered. The first volume discusses the esophagus, stomach and duodenum, liver, gallbladder and extrahepatic biliary ducts. The second volume covers the pancreas, spleen, small intestine, peritoneum, omenta, mesentery and colon. The third volume cov-

ers the anorectal tract, excisions of the rectum, herniae of the gastrointestinal tract and incisions in general.

It is, of course, impossible for any one work to cover completely such a varied subject, but Doctor Shackelford's effort is a most worthy one. Not only is surgical technique discussed thoroughly, but the basic physiology-pathology is so clearly explained that I hardly see how any general surgeon, from resident to professor, can fail to be fascinated by it. G. R.

Psychische Hygiene. Edited by Ernst Brezina and Erwin Stransky. Pp. 282. Vienna: Wilhelm Maudrich, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $8.25.

This book is an introduction into the vast field of mental hygiene. After a historical chapter (W. Holzer), there are chapters on the development of the field of mental hygiene (W. Beers), on the relationship of mental hygiene to clinical psychiatry (E. Stransky), to psychotherapy (H. Kogerer), to somatic hygiene (E. Brezina), to child psychiatry (H. Asperger), to geriatrics (E. Stransky), to sexual and mental problems (F. Stengel, A. Niedermeyer), to suicide (Menninger, Lerchenthal), to industrial problems (R. Jech), to criminologic problems (E. Stransky), to sociologic problems (Kogerer, Smekal-Huber) and to alcoholism (Kogerer). This text will probably serve well its purpose to introduce Austrian practitioners and social workers to these important problems.

E. S.

The Story of Medicine. By Kenneth Walker, M.A., M.B., F.R.C.S. Pp. 343; 51 ills. New York: Oxford University Press, 1955. Price, $6.00.

The author's purpose in writing this book appears to have been to produce something readable and attractive for lay consumption. In this he has fully succeeded. At the same time he has managed to give an adequate coverage of essentials. In the first part of the book the important medical discoveries are discussed in a fairly chronological order. Later sections are devoted to practical medical problems and so have a less personal aspect. There is some tendency, in the interest of readability, to overemphasize items that might catch the layman's interest and to gloss over important but less attractive items. A section on "Deficiency Diseases" includes not only the avitaminoses but all that the book contains about the endocrine organs. The name "Wassermann" is mispelled both in the text and the index. In speaking of the vicissitudes attending the introduction of vaccination against smallpox, the author refers to an American who recently inspired a three-volume biography as "a certain Mr. Cotton Mather." However, these are minor items. The layman will find the book instructive as well as very readable. R. K.

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M.D., Consultant in Medicine, Massachusetts General Hospital. American Lecture Series No. 242. Pp. 186; 35 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $5.50.

This little book contains much practical advice, not only for the general practitioner but also for the internist and the medical student, as an aid to the diagnosis and treatment of heart disease. It could have been written only by a past master in the field.

R. K.

Gestation. Transactions of the First Conference, March 9, 10, and 11, 1954, Princeton N. J. Edited by Louis B. Flexner, M.D., Professor and Chairman, Department of Anatomy, University of Pennsylvania School of Medicine. Pp. 238; 97 ills. including 4 color plates. New York: Josiah Macy, Jr. Foundation, 1955. Price, $5.00.

The first conference on Gestation which was sponsored by the Josiah Macy, Jr. Foundation and reported in this volume was limited to the structure and function of the placenta. The members of the conference were anatomists, physiologists, biologists, chemists, embryologists and obstetricians, each of whom had a particular interest and considerable experience with some specific phase of placental structure or function. This represents, therefore, the most authoritative current information on the placenta.

The material is presented informally as it was discussed in the conferences and though definite topics were assigned to specific individuals for presentation little of the text is comparable to the orderly presentation of material in the usual scientific paper. Rather, it consists of statements, challenges, explanations, arguments and presentation of work in progress or completed experiments concerning "The Functional Role of the Placenta," "Problems of Sugar Transport in the Placenta of

the Ungulate," "The Comparative Anatomy and Histology of the Placental Barrier" and an appendix on "Enzymes of the Human Placenta."

While there is a tremendous amount of material of great importance to the obstetrician it is difficult to segregate from the mass of fascinating but highly technical experimental material being discussed. J. W.

OPERATIVE CHOLANGIOGRAPHIE. TECHNIK, DIAGNOSTIK, PRAXIS. By PRIV. DOZ. DR. W. HESS, Basel. Pp. 201; 150 ills. Stuttgart: Georg Thieme Verlag, 1955. Price, $10.00.

THE incidence of gallstones is steadily rising and may reach 25% of the population. Operations on the biliary tract are, therefore, extremely frequent and, unfortunately, are followed by postoperative symptoms in about 15% of cases, complications due largely to residual stones or stenotic processes. The importance of thorough investigation of the biliary tract at the time of operation is obvious. The value of cholangiography at the time of operation is equally clear. This excellent monograph should, therefore, be most welcome. Its first portion deals with the basic principles of cholangiography; the second, with the technique of cholangiographic diagnosis; and the third, discusses the surgery of the biliary passages under cholangiographic control. The numerous illustrations are very well done. Those who read German will find this a useful text; indeed, it deserves to be translated into English. R. K.

THE PLASMA PROTEINS IN PREGNANCY. By HAROLD C. MACK, M.D., Chief, Department of Obstetrics and Gynecology, Harper Hospital; Associate Clinical Professor of Obstetrics and Gynecology, Wayne University. Pp. 118; 22 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $3.75.

THIS monograph is based upon data from the Research Laboratory of the Children's Fund of Michigan, a review of the literature and the author's own observations and extensive clinical experience over a period of years. It represents an attempt to present the most modern and accurate information concerning the changes in plasma proteins during normal pregnancy and to assess their role in the production of pregnancy complications.

The material is divided into 4 chapters devoted to a general discussion of the form, derivation, measurement and function of body proteins, and to the proteins during normal and abnormal pregnancies and in the fetus.

During normal pregnancy the protein concentration declines progressively and the albumin : globulin ratio is reversed. Similar but exaggerated changes have been observed with preeclampsia and as the toxemia becomes more severe the alteration is more pronounced. There are no clearly defined effects of maternal disease in the electrophoretic pattern of fetal blood. No definite conclusions can be drawn with regard to etiologic factors in any of the pregnancy complications.

The material is presented clearly and in an interesting and easily understandable style. This book should be studied by every individual interested in obstetrics because it will provide an excellent foundation which will help him evaluate many of the contradictory statements concerning nutrition which constantly appear in the literature. J. W.

AGEING: GENERAL ASPECTS. Ciba Foundation Colloquia on Ageing, Vol. 1. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., AND MARGARET P. CAMERON, M.A., A.B.L.S. Pp. 255; 38 ills. Boston: Little, Brown & Company, 1955. Price, $6.75.

THIS is the record of the first of a series of Colloquia on Ageing being sponsored by the Ciba Foundation in London and in which invited scientists from many parts of the world participate. This Colloquium was held in July, 1954, with 34 participants, including 9 from the United States and 12 from various other countries. The subjects discussed are chiefly in the field of pathological physiology and the psychological aspects of ageing. The material is of a high order of excellence and of particular value are the informal discussions by the participants after each of the twenty-eight formal presentations. All interested in the field of Geriatrics will welcome this volume. R. K.

AIRBORNE CONTAGION AND AIR HYGIENE. AN ECOLOGICAL STUDY OF DROPLET INFECTIONS. By WILLIAM FIRTH WELLS. Pp. 423; 85 ills. Cambridge: Harvard University Press, 1955. Price, $6.00.

THE author is an engineer by training. This background plus intense and persistent research over a period of almost 25 years has made Mr. Wells the world's leading authority on airborne infection. In the present volume he records practically all of the pertinent information of any significance. As far as this

reviewer knows, there is nothing else remotely like it in existence; and for this reason the author has made an important contribution to scientific literature.

Two unique features deserve special comment. It is actually two books within one cover and written at two different levels, one for the specialist, the other for the layman, and most biologists are laymen in this subject. These are not in juxtaposition but are woven together so cleverly that not a whit of continuity is lost. The theoretical biologist can concentrate upon the laws of physical chemistry determining aerodynamic phenomena, whereas the semi-layman may enjoy uninterruptedly the interesting story of how Wells and other researchers discovered the facts of air contagion and went on to develop present day methods of air hygiene.

The manner of presenting the basic principles in Part I is the second unusual feature. Each of eight chapters starts off with a postulate that is occasionally challenging and always incites curiosity; then comes the supportive data; and finally a recapitulation.

In spite of failure to find any reference to formaldehyde disinfection, this reviewer believes that Wells' book will be not only a study tool for the specialized epidemiologist but also a reference volume of great value to a great many workers in the health sciences ranging from industrial hygienists to hospital administrators and surgeons. E. S.

Differential Diagnosis. The Interpretation of Clinical Evidence. By A. McGehee Harvey, M.D., Professor of Medicine, Johns Hopkins University, and James Bordley, III, M.D., Director, Mary Imogene Bassett Hospital, Cooperstown, N. Y. Pp. 665. Philadelphia: W. B. Saunders Co., 1955. Price, $11.00.

This is not a systematic coverage of medical diagnosis as the title might imply. It presents a method of approach to the diagnosis of disease by means of the well-known device, the clinical pathological conference, and is based on the assumption that the student has the basic information on the symptom pictures of diseases. Of particular interest and significance is the excellent explanation of how the cases were selected and the systematic way in which they are to be analyzed. The 90 cases presented cover a wide range of presenting symptoms and topics such as cardiovascular disease, pain in the chest, sudden death, hematemesis, jaundice, lymphadenopathy, obscure fever. There are also 11 unknown cases to let the reader test his skill before he refers to the solutions at the end of the book. The clinical pathological conference is an excellent teaching device in spite of its obvious limitations. This volume is the C.P.C. at its best. It is heartily recommended to senior students and physicians and particularly to teachers who use such conferences with their students. R. K.

The Human Machine. Biological Sciences for the Armed Services. By Charles W. Shilling, Captain, Medical Corps, USN. Pp. 292; 156 ills. Annapolis: United States Naval Institute, 1955. Price, $5.00.

Originally intended for special hygiene instruction of midshipmen at the U. S. Naval Academy, this book gradually evolved into a text suitable for servicemen in general. It is equally appropriate for nonmedically oriented civilians who are interested in reading an authoritative, lucid discussion of the structure and physiology of the human body. There are also excellent sections on preventive maintenance and repair of the human machine, and the special health problems associated with underwater activity (submarines, deep-sea diving, underwater swimming); atomic, chemical, and biologic warfare; and aviation medicine. C. Z.

Systemic Associations and Treatment of Skin Diseases. By Kurt Wiener, M.D., Dermatologist, Mount Sinai Hospital, Deaconess Hospital, Milwaukee, Wis. Pp. 556; 90 ills. St. Louis: C. V. Mosby Co., 1955. Price, $17.00.

Dr. Wiener has put in his new book material which has needed correlation for a long time. At first sight it would appear that this volume is a revised edition of the book entitled, "Skin Manifestations of Internal Disorders (Dermadromes)," published by the C. V. Mosby Co. in 1947. However, in that publication Wiener described the cutaneous changes which accompany internal or systemic diseases. The systemic phenomenon associated with cutaneous diseases were not dealt with. The present work is concerned with this aspect of the relationship of dermatology and general medicine. There is some overlap in both books, especially when the cutaneous and systemic phases are of equal importance. Several diseases, such as lupus erythematosus and scleroderma, are given fuller discussion in the new text.

Syphilis is omitted, as in the first volume, because of lack of space for complete discussion. Systemic treatment of dermatoses is included. This embraces not only nontopical drugs but also indirect radiation therapy, diets and balneotherapy (spas). There is a short chapter on unorthodox methods. There is a satisfactory index and the illustrations are to the point. The language is generally excellent although there is an occasional slip, such as "tubercular" for "tuberculous" on page 28 (the word is correct on page 29), and the author documents practically every statement with a group of representative references usually including some of the very recent work. These references, in addition to those in English, largely because of the author's background, reflect his German training. The subject matter is covered most adequately although there are certain diseases, such as scabies, for example, which could have been included. A book of this type should help to raise the status of Dermatology among the various medical specialties. H. B.

POPULATION GENETICS. By CHING CHUN LI, Graduate School of Public Health, University of Pittsburgh. Pp. 366; 82 ills. Chicago: University of Chicago Press, 1955. Price, $10.00.

THIS is a general, systematic introduction to the genetics of populations. The author assumes only that the reader is familiar with the Mendelian laws and has an understanding of college algebra. In this manner he has avoided the formidable presentation which is often characteristic of discourses on this fundamental discipline. Various genetic theorems are presented in turn, with many useful figures and diagrams to aid the student. In addition, valuable notes and exercises are appended to each chapter.

Those concerned with the population problems of heredity and genetics will find this a broadly valuable text. C. Z.

LABORATORY IDENTIFICATION OF PATHOGENIC FUNGI SIMPLIFIED. By ELIZABETH L. HAZEN, PH.D., Associate Bacteriologist, and FRANK CURTIS REED, Laboratory Illustrator and Photographer. New York State Department of Health, Albany. Pp. 108; 22 ills. Springfield, Ill.: Charles C Thomas, 1955. Price, $5.50.

THE authors have produced a pictorial manual for laboratories engaged in diagnostic mycology. The text, which is the simplified part, consists essentially of descriptions of the excellent photographs. These show colonies and fungous elements, unstained and stained, in magnifications and forms most often encountered by the laboratorian. With few exceptions only morphological and cultural methods are included, but in diagnostic mycology this is usually enough. Perhaps it is all right to omit instructions of how clinical material should be prepared for microscopic examination and culturing because these can be found in many books on laboratory methodology, whereas photographs like these certainly cannot be. E. S.

HISTOLOGISCHE GESCHWULSTDIAGNOSTIK. SYSTEMATISCHE MORPHOLOGIE DER MENSCHLICHEN GESCHWÜLSTE ALS GRUNDLAGE FÜR DIE KLINISCHE BEURTEILUNG. By PROF. DR. A. VON ALBERTINI, University of Zurich. Pp. 544; 638 ills. Stuttgart: Georg Thieme Verlag, 1955 (Intercontinental Medical Book Corp., New York, U. S. Agents). Price, $23.40.

THIS book seems to be the first Surgical Pathology published in German that is comparable to several similar books available in the United States. It may be described as an aid in the histological diagnosis of the various tumors which occur in man. The book is well written and contains many excellent illustrations. Its shortcomings are that it is strictly morphological in approach, dynamic aspects such as etiology, histogenesis, clinical-pathological correlation or prognosis scarcely being touched upon. The interpretations and classifications offered by the author leave, therefore, much to be desired. As an aid in histological tumor diagnosis, however, the book is recommended to professional pathologists. W. E.

BIOCHEMISTRY AND PHYSIOLOGY OF PROTOZOA, VOLUME II. Edited by S. H. HUTNER AND ANDRE LWOFF. Pp. 388; illustrated. New York: Academic Press, Inc., 1955. Price, $9.00.

THE second of these basic volumes contains contributions by twelve outstanding investigators of protozoan organisms and their metabolism. There is a splendid introductory chapter by S. H. Hutner in which protozoa are considered as biochemical tools and as tools for phylogenetic study. This is followed by sections on the Comparative Biochemistry

of Flagellates; the Composition and Synthesis of the Starch of *Polytomella coeca;* the Nutrition of Ciliates; Encystment and Excystment of Protozoa; the Metabolism of Free-Living Ciliates; Mutualistic Intestinal Protozoa; Flagellates of Termites and Cryptocercus; Developmental Physiology of the Ameboid Slime Molds; Chemotherapy of Malaria, Piroplasmosis, Trypanosomiasis, and Leishmaniasis, and Comparative Studies on Amebae and Amebicides.

Students of comparative biochemistry and physiology, as well as protozoologists, will find much of interest and value in this book.

C. Z.

KLINISCHE ZYTOLOGIE DER THORAXKRANKHEITEN. By DR. MED. HEINZ GRUNZE. Pp. 190; 154 ills., 56 in color. Stuttgart: Ferdinand Enke Verlag, 1955. Price, Geheftet DM 56.; Ganzleinen DM 59.

THIS excellent book is based principally on more than 2,500 cytological studies of more than 600 patients with pulmonary disease. It contains comprehensive discussions of cytological techniques, cytodiagnostic criteria and results obtained with various effusions and aspirated materials from lungs, lymph nodes and spleen. The book is richly illustrated. More than 50 illustrations are in color. The plan of the author to describe the scope and the results of exfoliative cytology in diseases of the thorax has been realized in exemplary fashion. The book is highly recommended to all who are concerned with the diagnosis of pulmonary disease.

W. E.

NEW BOOKS

The Rural Hospital: Its Structure and Organization. By DR. R. F. BRIDGMAN, Deputy Director of Health of the Department of the Seine, France. Pp. 162; 21 ills. Geneva: World Health Organization, 1955. Price, $4.00.

THIS monograph is one of a series prepared by the World Health Organization as a guide for those confronted with the planning of a rural hospital. It is pointed out that such an institution is not only a place to care for the sick but should serve as the community's health center with outpatient clinics, welfare services and programs of health education of the public and disease control. The present volume is addressed particularly to countries that do not, as yet, possess a fully developed hospital network. It goes into considerable detail concerning architecture, equipment and staff needs, including medical, nursing, technical and administrative personnel. There are also discussed possible methods of financing and types of organization to suit different conditions. Also taken into consideration are tropical locations, primitive areas and various degrees of population density and advancement. The book should be of great value to many people in many places.

R. K.

The Effect of Sugar Supplements on Dental Caries in Children. By J. D. KING, MAY MELLANBY, H. H. STONES AND H. N. GREEN, Dental Research Committee of Medical Research Council (England), Special Report Series No. 288. Pp. 55; 4 ills. London: Her Majesty's Stationery Office, 1955. Price, 4 s.

THIS report will be of considerable interest to all concerned with the problem of dental caries in children. By contrast to the generally accepted idea in this country that the intake of sugar as such aids the initiation and spread of dental caries, the observations recorded in this report indicate that no such relationship exists within periods of time ranging up to two years.

W. N.

Foetal, Infant and Early Childhood Mortality. Vol. I., The Statistics. Pp. 137; 6 ills. New York: United Nations, 1954. Price, $1.50.

THIS book represents an effort to secure and to bring together comparative data on foetal and neonatal mortality (pregnancy wastage) and on mortality rates in infancy and early childhood (under 1 year and 1 to 4 years of life) for the years 1945–1949 in the various countries of the world. The methods of securing the data, their limitations and the problems of analyzing and interpreting them are explained. There is also a chapter dealing with the medical causes of the mortality. This volume and the second one listed below have considerable value in defining more explicitly the problems related to mortality in utero, in infancy and early childhood.

W. N.

Foetal, Infant and Early Childhood Mortality. Vol. II., Biological, Social and Economic Factors. Pp. 44; 4 ills. New York: United Nations, 1954. Price, $.40.

IN this volume there is an attempt to evaluate the underlying or nonmedical causes of the extensive wastage of life in utero and in early infancy and childhood throughout the world and to explain the marked differences in mortality rates in different countries in terms of biological, social and economic factors. There is also an attempt to interpret the probable economic and demographic costs to society of mortality in these age groups.

W. N.

Evaluation of 1954 Field Trials of Poliomyelitis Vaccine. Summary Report. American Journal of Public Health, Vol. 45, No. 5,

May, 1955. Pp. 63; illustrated. Ann Arbor, Michigan: Edwards Brothers, 1955.

THIS is the excellent and detailed report of the evaluation of the 1954 poliomyelitis vaccine trials on which the approval of Doctor Salk's vaccine by Doctor Francis and his group is based. R. K.

NEW EDITIONS

Roentgen Interpretation. By GEORGE W. HOLMES, M.D., AND LAURENCE L. ROBBINS, M.D., Massachusetts General Hospital. 8th ed. Pp. 525; 371 ills. Philadelphia: Lea & Febiger, 1955. Price, $10.00.

THIS is the eighth edition of an old friend which made its first appearance in 1919, written for "those in search of a working knowledge of roentgen interpretation." The present edition has new chapters on the heart, lungs and gastro-intestinal tract and changes on the examination of the abdomen and on fluoroscopic technique. The general character of previous editions has not been changed, this still being a presentation of essentials. For detailed understanding of any specific subject, reference to other works is necessary. The book covers the field and remains of value as a working basis for the student of diagnostic roentgenology. H. W.

The Mayo Clinic. By LUCY WILDER. 2nd ed. Pp. 69; profusely illustrated. Springfield, Ill.: Charles C Thomas, 1955. Price, $3.75.

MRS. WILDER, wife of Dr. Russell M. Wilder, former Chief of the Department of Medicine of the Mayo Foundation, presents a second edition of the original volume published in 1936 under the supervision of Drs. William J. and Charles H. Mayo. The present edition brings the history of the Mayo Clinic up-to-date. It should be of particular interest to former Fellows and Staff Members of that institution and to the many patients whose medical and surgical problems have been solved at the Mayo Clinic. J. L.

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DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa.

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